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STAFF REPORT to the NIDA DIRECTOR

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RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Peer Influences On Drug Self-Administration: An Econometric Analysis In Socially Housed Rats. Peitz GW, Strickland JC, Pitts EG, Foley M, Tonidandel S, Smith MA. Behav Pharmacol. 2013 Apr; 24: 114-123.

Social-learning theories of substance use propose that members of peer groups influence the drug use of other members by selectively modeling, reinforcing, and punishing either abstinence-related or drug-related behaviors. The objective of the present study was to examine the social influences on cocaine self-administration in isolated and socially housed rats, under conditions where the socially housed rats were tested simultaneously with their partner in the same chamber. To this end, male rats were obtained at weaning and housed in isolated or pair-housed conditions for 6 weeks. Rats were then implanted with intravenous catheters and cocaine self-administration was examined in custom-built operant conditioning chambers that allowed two rats to be tested simultaneously. For some socially housed subjects, both rats had simultaneous access to cocaine; for others, only one rat of the pair had access to cocaine. An econometric analysis was applied to the data, and the reinforcing strength of cocaine was measured by examining consumption (i.e. quantity demanded) and elasticity of demand as a function of price, which was manipulated by varying the dose and ratio requirements on a fixed ratio schedule of reinforcement. Cocaine consumption decreased as a function of price in all groups. Elasticity of demand did not vary across groups, but consumption was significantly lower in socially housed rats paired with a rat without access to cocaine. These data suggest that the presence of an abstaining peer decreases the reinforcing strength of cocaine, thus supporting the development of social interventions in drug abuse prevention and treatment programs.

Concurrent Choice For Social Interaction and Amphetamine Using Conditioned Place Preference In Rats: Effects Of Age and Housing Condition. Yates JR, Beckmann JS, Meyer AC, Bardo MT. Drug Alcohol Depend. 2013 May 1; 129: 240-246.

Social interaction can serve as a natural reward that attenuates drug reward in rats; however, it is unknown if age or housing conditions alter the choice between social interaction and drug. Individually- and pair-housed adolescent and adult male rats were tested using conditioned place preference (CPP) in separate experiments in which: (1) social interaction was conditioned against no social interaction; (2) amphetamine (AMPH; 1 mg/kg, s.c.) was conditioned against saline; or (3) social interaction was conditioned against AMPH. Social interaction CPP was obtained only in individually-housed adolescents, whereas AMPH CPP was obtained in both individually-housed adolescents and adults; however, the effect of AMPH was not statistically significant in pair-housed adults. When allowed to choose concurrently between compartments paired with either social interaction or AMPH, individually-housed adolescents preferred the compartment paired with social interaction, whereas pair-housed adolescents preferred the compartment paired with AMPH. Regardless of housing condition, adults showed a similar preference for the compartments paired with either social interaction or AMPH. Although some caution is needed in interpreting cross-experiment comparisons, the overall results suggest that individually-housed adolescents were most

sensitive to the rewarding effect of social interaction, and this hypersensitivity to social reward effectively competed with AMPH reward.

Pair Housing Differentially Affects Motivation To Self-Administer Cocaine In Male and Female Rats. Westenbroek C, Perry AN, Becker JB. Behav Brain Res. 2013 May 30; 252C: 68-71. Female rats exhibit greater intake and motivation to self-administer cocaine. In females but not males, isolation by itself is a stressor, which could lead to increased drug intake. Therefore, the authors hypothesized that social housing would buffer against stress and reduce the motivation to self-administer cocaine primarily in females. Male and female Sprague-Dawley rats were housed individually or in same-sex pairs. The individually housed rats and one of each pair were allowed to self-administer (SA) a low dose of cocaine (0.2mg/kg/inf) on a fixed ratio (FR1) schedule for one week. Motivation for cocaine SA was measured for an additional 2 weeks on a progressive ratio schedule. Isolated females had greater cocaine-intake on the FR1 schedule and greater motivation to take cocaine than males. Pair-housing in females, but not males, attenuated the motivation to take cocaine. Isolated females, but not males, showed escalation of their motivation to take cocaine, which was attenuated by pair housing of females. Concluding, the motivation to take cocaine escalates in females but not males, and pair-housing of females attenuates this escalation.

On the Persistence Of Cocaine-Induced Place Preferences and Aversions In Rats. Su, ZI, Santoostaroam A, Wenzel J, Ettenberg A. Psychopharmacology (Berl). 2013 Apr 9; Epub. Rats develop preferences for places associated with the immediate rewarding effects of cocaine and aversions for places paired with the drug's delayed negative effects. The motivation to seek cocaine should therefore depend upon the relative magnitude of these two opposing effects of the drug. The current study tested this notion by assessing the relative persistence of the positive and negative associations formed between environmental cues and the immediate or delayed effects of cocaine. Rats were administered 1.0 mg/kg intravenous cocaine and placed into a distinctive environment either immediately or 15-min after injection, alternating daily with pairings of a second environment with saline. After four drug-place and four saline-place pairings, rats were returned to their home cages for 1, 7, or 21 days after which a 15-min place preference test was conducted. In a second experiment, the effectiveness of a single reconditioning session (one drug-place and one saline-place pairing) to reactivate learned cocaine-place associations was assessed after 1 or 3 weeks of drug abstinence. Places associated with the immediate effects of cocaine were preferred (CPP), while places associated with the delayed effects of cocaine were avoided (CPA). The persistence of these effects differed with CPP remaining viable at 3 weeks of withdrawal, while CPA was no longer present after 1 week. Reconditioning with an additional cocaine-place pairing failed to reinstate the CPA. Cue-induced "relapse" of cocaine-seeking behavior may be fueled in part by an increased persistence of positive relative to negative associations with drug-paired stimuli.

Intravenous Prenatal Nicotine Exposure Increases Orexin Expression In the Lateral Hypothalamus and Orexin Innervation of the Ventral Tegmental Area In Adult Male Rats. Morgan AJ, Harrod SB, Lacy RT, Stanley EM, Fadel JR. Drug Alcohol Depend. 2013 May 7; Epub.

Prenatal tobacco smoke exposure is associated with alterations in motivated behavior in offspring, such as increased consumption of highly palatable foods and abused drugs. Animal models show that gestational nicotine (GN) exposure mediates changes in responding for sucrose and drug reward. A novel, intermittent low-dose intravenous (IV) exposure model was used to administer nicotine (0.05 mg/kg/injection) or saline 3 × /day to rats on gestational days 8–21. Two experiments investigated the effect of IV GN on (1) the habituation of spontaneous locomotor activity and on (2) sucrose reinforced responding in offspring. For the operant experiments, animals acquired fixed-ratio (FR-3) responding for sucrose, 26% (w/v), and were tested on varying concentrations (0, 3, 10, 30, and 56%; Latin-square) according to a FR-3, and then a progressive-ratio (PR) schedule. Male and female adult offspring were used. IV GN did not alter birth or growth weight, or the number of pups born. No between-group differences in habituation to spontaneous locomotor activity were observed. FR testing produced an inverted U-shaped response curve, and rats showed peak responding for 10% sucrose reinforcement. Neither gestation nor sex affected responding, suggesting equivalent sensitivity to varying sucrose concentrations. PR testing revealed that GN rats showed greater motivation for sucrose reinforcement relative to controls. A low-dose, IV GN exposure model resulted in increased motivation to respond for sucrose reinforcement in adult offspring. This suggests that using a low number of cigarettes throughout pregnancy will result in increased motivation for highly palatable foods in adult, and perhaps, adolescent offspring.

Effect Of Wheel-Running During Abstinence On Subsequent Nicotine-Seeking In Rats. Sanchez V, Moore CF, Brunzell DH, Lynch WJ. Psychopharmacology (Berl). 2013 Jun; 227: 403-411.

Exercise appears to be a promising non-pharmacological treatment for nicotine addiction that may be useful for the vulnerable adolescent population. The aim of this study is to determine if wheel-running, an animal model of aerobic exercise, during an abstinence period would decrease subsequent nicotine-seeking in rats that had extended access to nicotine self-administration during adolescence. Male adolescent rats (n=55) were trained to self-administer saline or nicotine infusions (5 or 10 μg/kg) under a fixed ratio 1 schedule with a maximum of 20 infusions/day beginning on postnatal day 30. After 5 days, access was extended to 23 h/day with unlimited infusions for a total of 10 days. After the last self-administration session, rats were moved to polycarbonate cages for a 10-day abstinence period where they either had access to a locked or unlocked running wheel for 2 h/day. Nicotine-seeking was examined following the 10th day of abstinence under a within-session extinction/cue-induced reinstatement paradigm. Intake was higher at the 10 μg/kg dose as compared to the 5 μg/kg dose; however, intake did not differ within doses prior to wheel assignment. Compared to saline controls, rats that self-administered nicotine at either dose showed a significant increase in drug-seeking during extinction, and consistent with our hypothesis, exercise during abstinence attenuated this effect. Nicotine led to modest but significant levels of cue-induced reinstatement; however, in this adolescent-onset model, levels were variable and not affected by exercise. The authors conclude that exercise may effectively reduce relapse vulnerability for adolescent-onset nicotine addiction.

Early Social Experience Is Critical For the Development Of Cognitive Control and Dopamine Modulation Of Prefrontal Cortex Function. Baarendse PJ, Counotte DS, O'Donnell P, Vanderschuren LJ. Neuropsychopharmacology. 2013 Jul; 38: 1485-1494.
Social experiences during youth are thought to be critical for proper social and cognitive development. Conversely, social insults during development can cause long-lasting behavioral impairments and increase the vulnerability for psychopathology later in life. To investigate the importance of social experience during the juvenile and early adolescent stage for the development of cognitive control capacities, rats were socially isolated from postnatal day 21 to 42 followed by re-socialization until they reached adulthood. Subsequently, two behavioral dimensions of impulsivity (impulsive action in the five-choice serial reaction time task (5-CSRTT) and impulsive choice in the delayed reward task) and decision making (in the rat gambling task) were assessed. In a separate group of animals, long-lasting cellular and synaptic changes in adult medial prefrontal cortex (PFC) pyramidal neurons were determined following social isolation. Juvenile and early adolescent social isolation resulted in impairments in impulsive action and decision making under novel or challenging circumstances. Moreover, socially isolated rats had a reduced response to enhancement of dopaminergic neurotransmission (using amphetamine or GBR12909) in the 5-CSRTT under challenging conditions. Impulsive choice was not affected by social isolation. These behavioral deficits were accompanied by a loss of sensitivity to dopamine of pyramidal neurons in the medial PFC. These data show long-lasting deleterious effects of early social isolation on cognitive control and its neural substrates. Alterations in prefrontal cognitive control mechanisms may contribute to the enhanced risk for psychiatric disorders induced by aberrations in the early social environment.

Paradoxical Tolerance To Cocaine After Initial Supersensitivity In Drug-Use-Prone Animals. Ferris MJ, Calipari ES, Melchior JR, Roberts DC, España RA, Jones SR. Eur J Neurosci. 2013 Jun 3; Epub.
There is great interest in outlining biological factors and behavioral characteristics that either predispose or predict vulnerability to substance use disorders. Response to an inescapable novel environment has been shown to predict a "drug-use-prone" phenotype that is defined by rapid acquisition of cocaine self-administration. Here, the authors showed that response to novelty can also predict the neurochemical and behavioral effects of acute and repeated cocaine in rats. They used cocaine self-administration under a fixed-ratio 1 schedule followed by fast-scan cyclic voltammetry in brain slices to measure subsecond dopamine (DA) release and uptake parameters in drug-use-prone and -resistant phenotypes. Despite no significant differences in stimulated release and uptake, animals with high responses to a novel environment had DA transporters that were more sensitive to cocaine-induced uptake inhibition, which corresponded to greater locomotor activating effects of cocaine. These animals also acquired cocaine self-administration more rapidly and, after 5 days of extended access cocaine self-administration, high-responding animals showed robust tolerance to DA uptake inhibition by cocaine. The effects of cocaine remained unchanged in animals with low novelty responses. Similarly, the rate of acquisition was negatively correlated with DA uptake inhibition by cocaine after self-administration. Thus, the authors showed that tolerance to the cocaine-induced inhibition of DA uptake coexists with a behavioral phenotype that is defined by increased preoccupation with cocaine as measured by rapid acquisition and early high intake.

Double Dissociation Between the Anterior Cingulate Cortex and Nucleus Accumbens Core In Encoding The Context Versus the Content Of Pavlovian Cocaine Cue Extinction.
Torregrossa MM, Gordon J, Taylor JR. J Neurosci. 2013 May 8; 33(19): 8370-8377.
One strategy proposed to treat addictive disorders is to extinguish the association between environmental stimuli (cues) and actions associated with drug use to reduce relapse. The context specificity of extinction learning, however, impairs the ability of addicts to generalize extinction training to the drug-taking context. The authors previously reported that the NMDA receptor partial agonist d-cycloserine administered after pavlovian extinction of cocaine cues in the nucleus accumbens core (NAc) reduced cue-induced renewal. Nevertheless, it was unclear whether this was due to disrupted contextual encoding of extinction or enhanced extinction consolidation. Thus, they examined the effect of the NMDA receptor antagonist d-AP5 on context encoding versus cue extinction learning. They also determined the role of the anterior cingulate cortex (ACC) in encoding the cue extinction memory or the context, due to its projections to NAc, and hypothesized the role in conflict monitoring and contextual modulation of decision making. Using rats, the authors observed that NMDA receptor antagonism in the NAc did not alter context encoding but did interfere with acquisition of the cue extinction memory, i.e., learning, conversely inactivation of the ACC reduced the contextual encoding of extinction but did not interfere with the acquisition or expression of extinction. The observed effects were not present in the absence of cue extinction training. Additionally, the contextual memory did not appear to be consolidated in the ACC as neither postsession inactivation nor protein synthesis inhibition impaired context-appropriate responding. These results have implications for overcoming the context specificity of extinction to treat psychiatric disorders including addiction.

Repeated In Vivo Exposure Of Cocaine Induces Long-Lasting Synaptic Plasticity In Hypocretin/Orexin-Producing Neurons In the Lateral Hypothalamus In Mice. Rao Y, Mineur YS, Gan G, Wang AH, Liu ZW, Wu X, Suyama S, de Lecea L, Horvath TL, Picciotto MR, Gao XB. J Physiol. 2013 Apr 1; 591(Pt 7):1951-1966.
Hypocretin (orexin), a neuropeptide synthesized exclusively in the perifornical/lateral hypothalamus, is critical for drug seeking and relapse, but it is not clear how the circuitry centred on hypocretin-producing neurons (hypocretin neurons) is modified by drugs of abuse and how changes in this circuit might alter behaviours related to drug addiction. In this study, the authors show that repeated, but not single, in vivo cocaine administration leads to a long-lasting, experience-dependent potentiation of glutamatergic synapses on hypocretin neurons in mice following a cocaine-conditioned place preference (CPP) protocol. The synaptic potentiation occurs postsynaptically and probably involves up-regulation of AMPA-type glutamate receptors on hypocretin neurons. Phosphorylation of cAMP response element-binding protein (CREB) is also significantly increased in hypocretin neurons in cocaine-treated animals, suggesting that CREB-mediated pathways may contribute to synaptic potentiation in these cells. Furthermore, the potentiation of synaptic efficacy in hypocretin neurons persists during cocaine withdrawal, but reverses to baseline levels after prolonged abstinence. Finally, the induction of long-term potentiation (LTP) triggered by a high-frequency stimulation is facilitated in hypocretin neurons in cocaine-treated mice, suggesting that long-lasting changes in synapses onto hypocretin neurons would probably be further potentiated by other stimuli (such as concurrent environmental cues) paired with the drug. In summary, the authors show here that hypocretin neurons undergo experience-dependent synaptic potentiation that is

distinct from that reported in other reward systems, such as the ventral tegmental area, following exposure to cocaine. These findings support the idea that the hypocretin system is important for behavioural changes associated with cocaine administration in animals and humans.

Synthesis and Structure-Activity Relationship Studies of O-Biphenyl-3-yl Carbamates as Peripherally Restricted Fatty Acid Amide Hydrolase Inhibitors. Moreno-Sanz G, Duranti A, Melzig L, Fiorelli C, Ruda GF, Colombano G, Mestichelli P, Sanchini S, Tontini A, Mor M, Bandiera T, Scarpelli R, Tarzia G, Piomelli D. J Med Chem. 2013 Jul 3; epub.
The peripherally restricted fatty acid amide hydrolase (FAAH) inhibitor URB937 (3, cyclohexylcarbamic acid 3'-carbamoyl-6-hydroxybiphenyl-3-yl ester) is extruded from the brain and spinal cord by the Abcg2 efflux transporter. Despite its inability to enter the central nervous system (CNS), 3 exerts profound antinociceptive effects in mice and rats, which result from the inhibition of FAAH in peripheral tissues and the consequent enhancement of anandamide signaling at CB_1 cannabinoid receptors localized on sensory nerve endings. In the present study, the authors examined the structure-activity relationships (SAR) for the biphenyl region of compound 3, focusing on the carbamoyl and hydroxyl groups in the distal and proximal phenyl rings. Their SAR studies generated a new series of peripherally restricted FAAH inhibitors and identified compound 35 (cyclohexylcarbamic acid 3'-carbamoyl-5-hydroxybiphenyl-3-yl ester) as the most potent brain-impermeant FAAH inhibitor disclosed to date.

In Vivo Characterization Of the Highly Selective Monoacylglycerol Lipase Inhibitor KML29: Antinociceptive Activity Without Cannabimimetic Side Effects. Ignatowska-Jankowska BM, Ghosh S, Crowe MS, Kinsey SG, Niphakis MJ, Abdullah RA, Tao Q, O'Neal ST, Walentiny DM, Wiley JL, Cravatt BF, Lichtman AH. Br J Pharmacol. 2013 Jul 12; Epub.
Since monoacylglycerol lipase (MAGL) has been firmly established as the predominant catabolic enzyme of the endocannabinoid 2-arachidonoylglycerol (2-AG), a great need has emerged for the development of highly selective MAGL inhibitors. Here, the authors tested the in vivo effects of one such compound, KML29. In the present study, the authors tested KML29 in murine inflammatory (i.e. carrageenan) and sciatic nerve injury pain models, as well as the diclofenac-induced gastric hemorrhage model. KML29 was also evaluated for cannabimimetic effects, including measurements of locomotor activity, body temperature, catalepsy, and cannabinoid interoceptive effects in the drug discrimination paradigm. KML29 attenuated carrageenan-induced paw edema and completely reversed carrageenan-induced mechanical allodynia. These effects underwent tolerance after repeated administration of high-dose KML29, which were accompanied by CB1 receptor desensitization. Acute or repeated KML29 administration increased 2-AG levels and concomitantly reduced arachidonic acid levels, but without elevating anandamide (AEA) levels in the whole brain. Furthermore, KML29 partially reversed allodynia in the sciatic nerve injury model and completely prevented diclofenac-induced gastric hemorrhages. CB1 and CB2 receptors played differential roles in these pharmacological effects of KML29. In contrast, KML29 did not elicit cannabimimetic effects, including catalepsy, hypothermia, and hypomotility. Although KML29 did not substitute for THC in C57BL/6J mice, it fully and dose-dependantly substituted for AEA in FAAH(‰/‰) mice, consistent with previous work showing that dual FAAH and MAGL inhibition produces THC-like subjective effects. These results indicate that

KML29, a highly selective MAGL inhibitor, reduces inflammatory and neuropathic nociceptive behavior without occurrence of cannabimimetic side effects.

Biological Active Analogues Of the Opioid Peptide Biphalin: Mixed α/β(3)-Peptides.
Mollica A, Pinnen F, Costante R, Locatelli M, Stefanucci A, Pieretti S, Davis P, Lai J, Rankin D, Porreca F, Hruby VJ. J Med Chem. 2013 Apr 25; 56(8): 3419-3423.
Natural residues of the dimeric opioid peptide Biphalin were replaced by the corresponding homo-β(3) amino acids. The derivative 1 containing hβ(3) Phe in place of Phe showed good μ- and δ-receptor affinities (Ki(δ) = 0.72 nM; Ki(μ) = 1.1 nM) and antinociceptive activity in vivo together with an increased enzymatic stability in human plasma.

Antinociceptive Effects Of Two Deltorphins Analogs In the Tail-Immersion Test In Rats.
Kotlinska JH, Gibula-Bruzda E, Witkowska E, Chung NN, Schiller PW, Izdebski J. Peptides. 2013 Jan; 39: 103-110.
The antinociceptive effects of analogs of deltorphins: cyclo(Nδ,Nδ-carbonyl-D-Orn2, Orn4)deltorphin (DEL-6) and deltorphin II N-(ureidoethyl)amide (DK-4) after intracerebroventricular (i.c.v.) administration were investigated in the tail-immersion test in rats. Morphine, the most commonly used μ-opioid receptors (MOR) agonist, was employed as a reference compound. The contribution of the MOR, δ-(DOR) and κ-opioid receptors (KOR) in antinociceptive effects of the deltorphins analogs was studies using selective antagonists of these receptors. The results indicated that DK-4 (5, 10 and 20 nmol) and DEL-6 (5, 10 and 20 nmol) were the most effective in alleviating thermal pain at the dose of 20 nmol. The antinociceptive potency of DEL-6 at the dose of 20 nmol was approximately equal but DK-4 at the dose of 20 nmol was less effective than morphine at the dose of 13 nmol. DOR antagonist - naltrindole (NTI, 5 nmol) very strongly and, to the lower extent MOR antagonist - β-funaltrexamine (β-FNA, 5 nmol), inhibited antinociceptive effect of DK-4 (20 nmol). In turn, β-FNA was more potent than NTI in inhibition of the antinociceptive effects of DEL-6. Co-administration of DEL-6 and morphine at doses of 5 nmol, which do not produce measurable antinociception, generated additive antinociceptive effect. Chronic intraperitoneal (i.p.) injection of morphine (9 days) displayed a marked analgesic tolerance to the challenge dose of morphine and a slight cross-tolerance to challenge doses of DEL-6 and DK-4, given i.c.v. These findings indicate that the new deltorphin analogs recruit DOR and MOR to attenuate the nociceptive response to acute thermal stimuli.

Involvement Of Dynorphin and Kappa Opioid Receptor In Yohimbine-Induced Reinstatement Of Heroin Seeking In Rats. Zhou Y, Leri F, Grella SL, Aldrich JV, Kreek MJ. Synapse. 2013 Jun; 67(6): 358-361.
The behavioral objective of these experiments was to investigate the potential of KOP-r receptor blockade to reduce heroin seeking when reinstatement was induced by Yoh. Although the main effects of Yoh on behaviors motivated by drugs of abuse are related to noradrenergic and HPA axis activation, Yohinduced reinstatement of cocaine and alcohol seeking also has a considerable serotonergic component (see recent review by Sinha et al., 2011). Nor-BNI (20 mg kg21, i.p.), a systemically active and selective KOP-r antagonist, significantly blocked Yoh-induced reinstatement. Consistent with the authors' finding, KOP-r antagonists have been found to reduce drug seeking induced by a variety of stressors, like foot-shock or forced swim, but not by drug priming with drugs of abuse (Aldrich et al., 2009; Beardsley et al., 2005). It is

unlikely that this resulted from a suppression of general activity because the well-established anxiolytic profile of the compound is based on performance in tests where reductions in anxiety are indicated by enhanced motor activity (Knoll and Carlezon, 2010). Therefore, these results suggest that Dyn activation of KOP-r receptors in response to Yoh plays a critical role in modulating the effects of Yoh stress on reinstatement of heroin seeking. To the authors' knowledge, this is the first demonstration of KOP-r involvement in heroin seeking behavior.

Designing Bifunctional NOP Receptor-Mu Opioid Receptor Ligands From NOP Receptor-Selective Scaffolds. Part I. Zaveri NT, Jiang F, Olsen C, Polgar WE, Toll L. Bioorg Med Chem Lett. 2013 Jun 1; 23(11): 3308-3313.
The nociceptin receptor (NOP) and its endogenous agonist, nociceptin/orphanin FQ (N/OFQ), members of the opioid receptor and peptide families respectively, modulate the pharmacological effects of classical opioids, particularly opioid-induced reward and nociception. The authors hypothesized that compounds containing both NOP and opioid receptor activity in a single molecule may have useful pharmacological profiles as non-addicting analgesics or as drug abuse medications. They report here their forays into the structure-activity relationships for discovering 'bifunctional' NOP-mu opioid receptor (MOP) ligands, starting from their NOP-selective scaffolds. This initial SAR suggests pharmacophoric elements that may be modified to modulate/increase opioid affinity, while maintaining high affinity for the NOP receptor, to result in potent bifunctional small-molecule NOP/MOP ligands.

Development of κ Opioid Receptor Antagonists. Carroll FI, Carlezon WA Jr. J Med Chem. 2013 Mar 28; 56(6): 2178-2195.
κ opioid receptors (KORs) belong to the G-protein-coupled class of receptors (GPCRs). They are activated by the endogenous opioid peptide dynorphin (DYN) and expressed at particularly high levels within brain areas implicated in modulation of motivation, emotion, and cognitive function. Chronic activation of KORs in animal models has maladaptive effects including increases in behaviors that reflect depression, the propensity to engage in drug-seeking behavior, and drug craving. The fact that KOR activation has such a profound influence on behaviors often triggered by stress has led to interest in selective KOR antagonists as potential therapeutic agents. This Perspective provides a description of preclinical research conducted in the development of several different classes of selective KOR antagonists, a summary of the clinical studies conducted thus far, and recommendations for the type of work needed in the future to determine if these agents would be useful as pharmacotherapies for neuropsychiatric illness.

Retrodialysis Of N/OFQ Into the Nucleus Accumbens Shell Blocks Cocaine-Induced Increases In Extracellular Dopamine and Locomotor Activity. Vazquez-DeRose J, Stauber G, Khroyan TV, Xie XS, Zaveri NT, Toll L. Eur J Pharmacol. 2013 Jan 15; 699(1-3): 200-206.
Nociceptin (N/OFQ) has been implicated in a variety of neurological disorders, most notably in reward processes and drug abuse. N/OFQ suppresses extracellular dopamine in the nucleus accumbens (NAc) after intracerebroventricular injection. This study sought to examine the effects of retrodialyzed N/OFQ on the cocaine-induced increase in extracellular dopamine levels in the NAc, as well as locomotor activity, in freely moving rats. 1.0μM, 10μM, and 1mM N/OFQ, in the NAc shell, significantly suppressed the cocaine-induced dopamine

increase in the NAc, while N/OFQ alone had no significant effect on dopamine levels. Co-delivery of the selective NOP receptor antagonist SB612111 ([(-)-cis-1-Methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol] reversed the N/OFQ suppression of cocaine-induced dopamine in the NAc, suggesting that this is an NOP receptor-mediated effect. Using a novel system to assess locomotion, the authors measured various motor activities of the animals with simultaneous microdialysis from the home cage. Cocaine produced an expected increase in total activity, including horizontal movement and rearing behavior. Retrodialysis of N/OFQ with cocaine administration affected all motor activities, initially showing no effect on behavior, but over time inhibiting cocaine-induced motor behaviors. These results suggest that N/OFQ can act directly in the NAc shell to block cocaine-induced increases in extracellular dopamine levels. Extracellular dopamine and locomotor activity can be dissociated within the NAc and may reflect motor output differences in shell versus core regions of the NAc. These studies confirm the widespread involvement of NOP receptors in drug addiction and further validate the utility of an NOP receptor agonist as a medication for treatment of drug addiction

Neoclerodanes As Atypical Opioid Receptor Ligands. Prisinzano TE. J Med Chem. 2013 May 9; 56(9): 3435-3443.
The neoclerodane diterpene salvinorin A is the major active component of the hallucinogenic mint plant Salvia divinorum Epling and Játiva (Lamiaceae). Since the finding that salvinorin A exerts its potent psychotropic actions through the activation of opioid receptors, the site of action of morphine and related analogues, there has been much interest in elucidating the underlying mechanisms behind its effects. These effects are particularly remarkable because (1) salvinorin A is the first reported non-nitrogenous opioid receptor agonist and (2) its effects are not mediated through the previously investigated targets of psychotomimetics. This Perspective outlines our research program, illustrating a new direction to the development of tools to further elucidate the biological mechanisms of drug tolerance and dependence. The information gained from these efforts is expected to facilitate the design of novel agents to treat pain, drug abuse, and other central nervous system disorders.

Ligand/Kappa-Opioid Receptor Interactions: Insights From the X-Ray Crystal Structure. Martinez-Mayorga K, Byler KG, Yongye AB, Giulianotti MA, Dooley CT, Houghten RA. Eur J Med Chem. 2013 May 30; 66C: 114-121.
During the past five years, the three-dimensional structures of 14 different G-protein coupled receptors (GPCRs) have been resolved by X-ray crystallography. The most recently published structures, those of the opioid receptors (ORs), are remarkably important in pain modulation, drug addiction, and mood disorders. These structures, confirmed previously proposed key interactions conferring potency and antagonistic properties, including the well-known interaction with Asp138, conserved in all aminergic GPCRs. In addition, crystallization of the opioid receptors highlighted the potential function of the ECL2 and ICL2 loops. The authors have previously reported a set of potent and selective kappa opioid receptor peptide agonists, of which ff(D-nle)r-NH_2 is among the most potent and selective ones. These peptides were identified from the deconvolution of a 6,250,000 tetrapeptide combinatorial library. A derivative of this set is currently the subject of a phase 2 clinical trial in the United States. In this work, the authors describe comparative molecular modeling studies of kappa-OR peptide agonists with the co-crystallized antagonist, JDTic, and also report structure-activity

relationships of 23 tetrapeptides. The overall binding and contact interactions are sound and interactions known to favor selectivity and potency were observed. Additional modeling studies will reveal conformational changes that the kappa-OR undergoes upon binding to these peptide agonists.

Class I HDAC Inhibition Blocks Cocaine-Induced Plasticity By Targeted Changes In Histone Methylation. Kennedy PJ, Feng J, Robison AJ, Maze I, Badimon A, Mouzon E, Chaudhury D, Damez-Werno DM, Haggarty SJ, Han MH, Bassel-Duby R, Olson EN, Nestler EJ. Nat Neurosci. 2013 Apr; 16(4): 434-440.
Induction of histone acetylation in the nucleus accumbens (NAc), a key brain reward region, promotes cocaine-induced alterations in gene expression. Histone deacetylases (HDACs) tightly regulate the acetylation of histone tails, but little is known about the functional specificity of different HDAC isoforms in the development and maintenance of cocaine-induced plasticity, and previous studies of HDAC inhibitors report conflicting effects on cocaine-elicited behavioral adaptations. Here the authors demonstrate that specific and prolonged blockade of HDAC1 in NAc of mice increased global levels of histone acetylation, but also induced repressive histone methylation and antagonized cocaine-induced changes in behavior, an effect mediated in part through a chromatin-mediated suppression of GABAA receptor subunit expression and inhibitory tone on NAc neurons. These findings suggest a new mechanism by which prolonged and selective HDAC inhibition can alter behavioral and molecular adaptations to cocaine and inform the development of therapeutics for cocaine addiction.

Conformational Biosensors Reveal GPCR Signalling From Endosomes. Irannejad R, Tomshine JC, Tomshine JR, Chevalier M, Mahoney JP, Steyaert J, Rasmussen SG, Sunahara RK, El-Samad H, Huang B, von Zastrow M. Nature. 2013 Mar 28; 495(7442): 534-538.
A long-held tenet of molecular pharmacology is that canonical signal transduction mediated by G-protein-coupled receptor (GPCR) coupling to heterotrimeric G proteins is confined to the plasma membrane. Evidence supporting this traditional view is based on analytical methods that provide limited or no subcellular resolution. It has been subsequently proposed that signalling by internalized GPCRs is restricted to G-protein-independent mechanisms such as scaffolding by arrestins, or GPCR activation elicits a discrete form of persistent G protein signalling, or that internalized GPCRs can indeed contribute to the acute G-protein-mediated response. Evidence supporting these various latter hypotheses is indirect or subject to alternative interpretation, and it remains unknown if endosome-localized GPCRs are even present in an active form. Here the authors describe the application of conformation-specific single-domain antibodies (nanobodies) to directly probe activation of the β2-adrenoceptor, a prototypical GPCR, and its cognate G protein, Gs (ref. 12), in living mammalian cells. They show that the adrenergic agonist isoprenaline promotes receptor and G protein activation in the plasma membrane as expected, but also in the early endosome membrane, and that internalized receptors contribute to the overall cellular cyclic AMP response within several minutes after agonist application. These findings provide direct support for the hypothesis that canonical GPCR signalling occurs from endosomes as well as the plasma membrane, and suggest a versatile strategy for probing dynamic conformational change in vivo.

SMARCA3, A Chromatin-Remodeling Factor, Is Required For P11-Dependent Antidepressant Action. Oh YS, Gao P, Lee KW, Ceglia I, Seo JS, Zhang X, Ahn JH, Chait BT, Patel DJ, Kim Y, Greengard P. Cell. 2013 Feb 14; 152(4): 831-843.
p11, through unknown mechanisms, is required for behavioral and cellular responses to selective serotonin reuptake inhibitors (SSRIs). The authors show that SMARCA3, a chromatin-remodeling factor, is a target for the p11/annexin A2 heterotetrameric complex. Determination of the crystal structure indicates that SMARCA3 peptide binds to a hydrophobic pocket in the heterotetramer. Formation of this complex increases the DNA-binding affinity of SMARCA3 and its localization to the nuclear matrix fraction. In the dentate gyrus, both p11 and SMARCA3 are highly enriched in hilar mossy cells and basket cells. The SSRI fluoxetine induces expression of p11 in both cell types and increases the amount of the ternary complex of p11/annexin A2/SMARCA3. SSRI-induced neurogenesis and behavioral responses are abolished by constitutive knockout of SMARCA3. These studies indicate a central role for a chromatin-remodeling factor in the SSRI/p11 signaling pathway and suggest an approach to the development of improved antidepressant therapies.

The Neuron-Specific Chromatin Regulatory Subunit BAF53b Is Necessary For Synaptic Plasticity and Memory. Vogel-Ciernia A, Matheos DP, Barrett RM, Kramár EA, Azzawi S, Chen Y, Magnan CN, Zeller M, Sylvain A, Haettig J, Jia Y, Tran A, Dang R, Post RJ, Chabrier M, Babayan AH, Wu JI, Crabtree GR, Baldi P, Baram TZ, Lynch G, Wood MA. Nat Neurosci. 2013 May; 16(5): 552-561.
Recent exome sequencing studies have implicated polymorphic Brg1-associated factor (BAF) complexes (mammalian SWI/SNF chromatin remodeling complexes) in several human intellectual disabilities and cognitive disorders. However, it is currently unknown how mutations in BAF complexes result in impaired cognitive function. Postmitotic neurons express a neuron-specific assembly, nBAF, characterized by the neuron-specific subunit BAF53b. Mice harboring selective genetic manipulations of BAF53b have severe defects in long-term memory and long-lasting forms of hippocampal synaptic plasticity. The authors rescued memory impairments in BAF53b mutant mice by reintroducing BAF53b in the adult hippocampus, which suggests a role for BAF53b beyond neuronal development. The defects in BAF53b mutant mice appeared to derive from alterations in gene expression that produce abnormal postsynaptic components, such as spine structure and function, and ultimately lead to deficits in synaptic plasticity. These results provide new insight into the role of dominant mutations in subunits of BAF complexes in human intellectual and cognitive disorders.

HDAC3 Is A Negative Regulator Of Cocaine-Context-Associated Memory Formation. Rogge GA, Singh H, Dang R, Wood MA. J Neurosci. 2013 Apr 10; 33(15): 6623-6632.
Cocaine-induced neuroplasticity mediated by histone acetylating and deacetylating enzymes may contribute to addiction-like behaviors. For example, overexpression of histone deacetylases (HDACs) 4 or 5 in the nucleus accumbens suppresses cocaine-induced conditioned place preference (CPP) acquisition in mice. HDAC4 and HDAC5 are known to interact with HDAC3, but the role of HDAC3 in cocaine-induced behaviors has never been examined. In this study, the authors address the hypothesis that HDAC3 is a negative regulator of cocaine-context-associated memory formation in mice. They examined the role of HDAC3 during the conditioning phase of CPP, when the mouse has the opportunity to form an associative memory between the cocaine-paired context and the subjective effects of cocaine.

To address this hypothesis, Hdac3(flox/flox) and Hdac3(+/+) mice (generated from a C57BL/6 background) were infused into the nucleus accumbens with adeno-associated virus expressing Cre recombinase to create focal, homozygous Hdac3 deletions. Hdac3(flox/flox) mice exhibit significantly enhanced CPP acquisition, which is correlated with increased gene expression during the consolidation phase of acquisition. Increased gene expression of c-Fos and Nr4a2 is correlated with decreased HDAC3 occupancy and increased histone H4 lysine 8 acetylation at their promoters. The results from this study demonstrate that HDAC3 negatively regulates cocaine-induced CPP acquisition.

Injectable, Cellular-Scale Optoelectronics With Applications For Wireless Optogenetics. Kim TI, McCall JG, Jung YH, Huang X, Siuda ER, Li Y, Song J, Song YM, Pao HA, Kim RH, Lu C, Lee SD, Song IS, Shin G, Al-Hasani R, Kim S, Tan MP, Huang Y, Omenetto FG, Rogers JA, Bruchas MR. Science. 2013 Apr 12; 340(6129): 211-216.
Successful integration of advanced semiconductor devices with biological systems will accelerate basic scientific discoveries and their translation into clinical technologies. In neuroscience generally, and in optogenetics in particular, the ability to insert light sources, detectors, sensors, and other components into precise locations of the deep brain yields versatile and important capabilities. Here, the authors introduce an injectable class of cellular-scale optoelectronics that offers such features, with examples of unmatched operational modes in optogenetics, including completely wireless and programmed complex behavioral control over freely moving animals. The ability of these ultrathin, mechanically compliant, biocompatible devices to afford minimally invasive operation in the soft tissues of the mammalian brain foreshadow applications in other organ systems, with potential for broad utility in biomedical science and engineering.

Exploring Long-Range Genome Interactions Using the Washu Epigenome Browser. Zhou X, Lowdon RF, Li D, Lawson HA, Madden PA, Costello JF, Wang T. Nat Methods. 2013 May; 10(5): 375-376.
Eukaryotic chromosomes are a highly organized three-dimensional entity folded through a tightly regulated process with important functions that include bringing distal regulatory elements into the vicinity of their target gene promoters and arranging the chromosomes into distinct compartments. Recent technological innovations, including chromosome conformation capture carbon copy (5C), Hi-C and chromatin interaction analysis by paired-end tag sequencing (ChIA-PET), have facilitated the discovery of chromosomal organization principles and folding architectures at unprecedented scales and resolution. Each technology also comes with corresponding computational tools to process and visualize its specific data type. However, visualizing and navigating long-range interaction data, as well as integrating these interactions with other epigenomics data, remains a much-desired capability and a daunting challenge.

The Evolution Of Lineage-Specific Regulatory Activities In the Human Embryonic Limb. Cotney J, Leng J, Yin J, Reilly SK, Demare LE, Emera D, Ayoub AE, Rakic P, Noonan JP. Cell. 2013 Jul 3; 154(1): 185-196.
The evolution of human anatomical features likely involved changes in gene regulation during development. However, the nature and extent of human-specific developmental regulatory functions remain unknown. The authors obtained a genome-wide view of cis-regulatory

evolution in human embryonic tissues by comparing the histone modification H3K27ac, which provides a quantitative readout of promoter and enhancer activity, during human, rhesus, and mouse limb development. Based on increased H3K27ac, the authors find that 13% of promoters and 11% of enhancers have gained activity on the human lineage since the human-rhesus divergence. These gains largely arose by modification of ancestral regulatory activities in the limb or potential co-option from other tissues and are likely to have heterogeneous genetic causes. Most enhancers that exhibit gain of activity in humans originated in mammals. Gains at promoters and enhancers in the human limb are associated with increased gene expression, suggesting they include molecular drivers of human morphological evolution.

Multigenerational Effects Of Adolescent Morphine Exposure On Dopamine D2 Receptor Function. Byrnes JJ, Johnson NL, Carini LM, Byrnes EM. Psychopharmacology (Berl). 2013 May; 227(2): 263-272.

The use and misuse of prescription opiates in adolescent populations, and in particular, adolescent female populations, has increased dramatically in the past two decades. Given the significant role that opioids play in neuroendocrine function, exposure to opiates during this critical developmental period could have significant consequences for the female, as well as her offspring. In the current set of studies, the authors utilized the female rat to model the transgenerational impact of adolescent opiate exposure. They examined locomotor sensitization in response to the dopamine D2/D3 receptor agonist quinpirole in the adult male progeny (F1 and F2 generations) of females exposed to morphine during adolescence. All females were drug-free for at least 3 weeks prior to conception, eliminating the possibility of direct fetal exposure to morphine. Both F1 and F2 progeny of morphine-exposed females demonstrated attenuated locomotor sensitization following repeated quinpirole administration. These behavioral effects were coupled with increased quinpirole-induced corticosterone secretion and upregulated kappa opioid receptor and dopamine D2 receptor (D2R) gene expression within the nucleus accumbens. These results suggest significant modifications in response to repeated D2R activation in the progeny of females exposed to opiates during adolescence. Given the significant role that the D2R plays in psychopathology, adolescent opiate exposure could shift the vulnerability of future offspring to psychological disorders, including addiction. Moreover, that effects are also observed in the F2 generation suggests that adolescent opiate exposure can trigger transgenerational epigenetic modifications impacting systems critical for motivated behavior.

An Intronic Variant in OPRD1 Predicts Treatment Outcome for Opioid Dependence in African-Americans. Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Neuropsychopharmacology. 2013 Apr 23. [Epub ahead of print].

Although buprenorphine and methadone are both effective treatments for opioid dependence, their efficacy can vary significantly among patients. Genetic differences may explain some of the variability in treatment outcome. Understanding the interactions between genetic background and pharmacotherapy may result in more informed treatment decisions. This study is a pharmacogenetic analysis of the effects of genetic variants in OPRD1, the gene encoding the δ-opioid receptor, on the prevalence of opioid-positive urine tests in African-Americans (n=77) or European-Americans (n=566) undergoing treatment for opioid dependence. Patients were randomly assigned to treatment with either methadone or buprenorphine/naloxone

(Suboxone) over a 24-week open-label clinical trial, in which illicit opioid use was measured by weekly urinalysis. In African-Americans, the intronic SNP rs678849 predicted treatment outcome for both medications. Methadone patients with the CC genotype were less likely to have opioid-positive urine tests than those in the combined CT and TT genotypes group (relative risk (RR)=0.52, 95% confidence interval (CI)=0.44-0.60, p=0.001). In the buprenorphine treatment group, however, individuals with the CC genotype were more likely to have positive opioid drug screens than individuals in the combined CT and TT genotypes group (RR=2.17, 95% CI=1.95-2.68, p=0.008). These findings indicate that the genotype at rs678849 predicts African-American patient response to two common treatments for opioid dependence, suggesting that matching patients to treatment type based on the genotype at this locus may improve overall treatment efficacy. This observation requires confirmation in an independent population.

Behavioral and Structural Responses To Chronic Cocaine Require A Feedforward Loop Involving ΔFosB and Calcium/Calmodulin-Dependent Protein Kinase II In the Nucleus Accumbens Shell. Robison AJ, Vialou V, Mazei-Robison M, Feng J, Kourrich S, Collins M, Wee S, Koob G, Turecki G, Neve R, Thomas M, Nestler EJ. J Neurosci. 2013 Mar 6; 33(10): 4295-4307. The transcription factor ΔFosB and the brain-enriched calcium/calmodulin-dependent protein kinase II (CaMKIIα) are induced in the nucleus accumbens (NAc) by chronic exposure to cocaine or other psychostimulant drugs of abuse, in which the two proteins mediate sensitized drug responses. Although ΔFosB and CaMKIIα both regulate AMPA glutamate receptor expression and function in NAc, dendritic spine formation on NAc medium spiny neurons (MSNs), and locomotor sensitization to cocaine, no direct link between these molecules has to date been explored. Here, the authors demonstrate that ΔFosB is phosphorylated by CaMKIIα at the protein-stabilizing Ser27 and that CaMKII is required for the cocaine-mediated accumulation of ΔFosB in rat NAc. Conversely, they show that ΔFosB is both necessary and sufficient for cocaine induction of CaMKIIα gene expression in vivo, an effect selective for D1-type MSNs in the NAc shell subregion. Furthermore, induction of dendritic spines on NAc MSNs and increased behavioral responsiveness to cocaine after NAc overexpression of ΔFosB are both CaMKII dependent. Importantly, they demonstrate for the first time induction of ΔFosB and CaMKII in the NAc of human cocaine addicts, suggesting possible targets for future therapeutic intervention. These data establish that ΔFosB and CaMKII engage in a cell-type- and brain-region-specific positive feedforward loop as a key mechanism for regulating the reward circuitry of the brain in response to chronic cocaine.

Extrasynaptic Targeting of NMDA Receptors Following D1 Dopamine Receptor Activation and Cocaine Self-Administration. Ortinski PI, Turner JR, Pierce RC. J Neurosci. 2013 May 29; 33(22): 9451-9461.
The authors previously showed that after repeated exposure to cocaine, D1-like dopamine receptor (D1DR) stimulation reverses plastic changes of AMPA receptor-mediated signaling in the nucleus accumbens shell. However, there is little information on the impact of cocaine self-administration on D1-NMDA receptor interactions in this brain region. Here, using whole-cell patch-clamp recordings, they assessed whether cocaine self-administration alters the effects of D1DR stimulation on synaptic and extrasynaptic NMDA receptors (NMDARs). In slices from cocaine-naive rats, pretreatment with a D1DR agonist decreased synaptic NMDAR-mediated currents and increased the contribution of extrasynaptic NMDARs. In

contrast, neither cocaine self-administration alone nor cocaine experience followed by D1DR stimulation had an effect on synaptic or extrasynaptic NMDAR signaling. Activation of extrasynaptic NMDARs relies on the availability of extracellular glutamate, which is regulated primarily by glutamate transporters. In cocaine-experienced animals, relative to cocaine-naive rats, administration of a glutamate reuptake blocker, dl-threo-β-benzyloxyaspartic acid, revealed increased extrasynaptic NMDAR activity and stronger baseline activity of glutamate uptake transporters. In cocaine-naive rats, the D1DR-mediated increase in extrasynaptic NMDAR signaling was independent of the activity of glutamate reuptake transporters. Together, these results indicate that cocaine experience blunts the influence of D1DRs on synaptic and extrasynaptic NMDAR signaling. Additionally, prior cocaine self-administration limits activation of the extrasynaptic NMDAR pool by increasing glutamate reuptake. These findings outline a pattern of adaptive interactions between D1DRs and NMDARs in the nucleus accumbens shell and demonstrate upregulation of extrasynaptic NMDAR signaling as a novel consequence of cocaine self-administration.

Opposing Catecholamine Changes In the Bed Nucleus Of the Stria Terminalis During Intracranial Self-Stimulation and Its Extinction. Park J, Bucher ES, Fontillas K, Owesson-White C, Ariansen JL, Carelli RM, Wightman RM. Biol Psychiatry. 2013 Jul 1; 74(1): 69-76. While studies suggest that both dopamine and norepinephrine neurotransmission support reinforcement learning, the role of dopamine has been emphasized. As a result, little is known about norepinephrine signaling during reward learning and extinction. Both dopamine and norepinephrine projections innervate distinct regions of the bed nucleus of the stria terminalis (BNST), a structure that mediates behavioral and autonomic responses to stress and anxiety. The authors investigated whether norepinephrine release in the ventral BNST (vBNST) and dopamine release in the dorsolateral BNST (dlBNT) correlate with reward learning during intracranial self-stimulation (ICSS). Using fast-scan cyclic voltammetry, norepinephrine concentration changes in the vBNST
(n = 12 animals) during ICSS were compared with dopamine changes in the dlBNST (n = 7 animals) and nucleus accumbens (NAc) (n = 5 animals). Electrical stimulation was in the ventral tegmental area/substantia nigra region. Whereas dopamine release was evoked by presentation of a cue predicting reward availability in both dlBNST and NAc, cue-evoked norepinephrine release did not occur in the vBNST. Release of both catecholamines was evoked by the electrical stimulation. Extracellular changes in norepinephrine were also studied during extinction of ICSS and compared with results obtained for dopamine. During extinction of ICSS, norepinephrine release in the vBNST occurred at the time where the stimulation was anticipated, whereas dopamine release transiently decreased. The data demonstrate that norepinephrine release in the vBNST differs from dopamine release in the dlBNST and the NAc in that it signals the absence of reward rather than responding to reward predictive cues.

Kappa Opioid Receptors Regulate Stress-Induced Cocaine Seeking and Synaptic Plasticity. Graziane NM, Polter AM, Briand LA, Pierce RC, Kauer JA. Neuron. 2013 Mar 6; 77(5): 942-954. Stress facilitates reinstatement of addictive drug seeking in animals and promotes relapse in humans. Acute stress has marked and long-lasting effects on plasticity at both inhibitory and excitatory synapses on dopamine neurons in the ventral tegmental area (VTA), a key region necessary for drug reinforcement. Stress blocks long-term potentiation at GABAergic synapses on dopamine neurons in the VTA (LTPGABA), potentially removing a

normal brake on activity. Here the authors show that blocking kappa opioid receptors (KORs) prior to forced-swim stress rescues LTPGABA. In contrast, blocking KORs does not prevent stress-induced potentiation of excitatory synapses nor morphine-induced block of LTPGABA. Using a kappa receptor antagonist as a selective tool to test the role of LTPGABA in vivo, the authors find that blocking KORs within the VTA prior to forced-swim stress prevents reinstatement of cocaine seeking. These results suggest that KORs may represent a useful therapeutic target for treatment of stress-triggered relapse in substance abuse.

Distinct Extended Amygdala Circuits For Divergent Motivational States. Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, Kash TL, Stuber GD. Nature. 2013 Apr 11; 496(7444): 224-228.
The co-morbidity of anxiety and dysfunctional reward processing in illnesses such as addiction and depression suggests that common neural circuitry contributes to these disparate neuropsychiatric symptoms. The extended amygdala, including the bed nucleus of the stria terminalis (BNST), modulates fear and anxiety, but also projects to the ventral tegmental area (VTA), a region implicated in reward and aversion, thus providing a candidate neural substrate for integrating diverse emotional states. However, the precise functional connectivity between distinct BNST projection neurons and their postsynaptic targets in the VTA, as well as the role of this circuit in controlling motivational states, have not been described. Here the authors record and manipulate the activity of genetically and neurochemically identified VTA-projecting BNST neurons in freely behaving mice. Collectively, aversive stimuli exposure produced heterogeneous firing patterns in VTA-projecting BNST neurons. By contrast, in vivo optically identified glutamatergic projection neurons displayed a net enhancement of activity to aversive stimuli, whereas the firing rate of identified GABAergic (ýý-aminobutyric acid-containing) projection neurons was suppressed. Channelrhodopsin-2-assisted circuit mapping revealed that both BNST glutamatergic and GABAergic projections preferentially innervate postsynaptic non-dopaminergic VTA neurons, thus providing a mechanistic framework for in vivo circuit perturbations. In vivo photostimulation of BNST glutamatergic projections resulted in aversive and anxiogenic behavioural phenotypes. Conversely, activation of BNST GABAergic projections produced rewarding and anxiolytic phenotypes, which were also recapitulated by direct inhibition of VTA GABAergic neurons. These data demonstrate that functionally opposing BNST to VTA circuits regulate rewarding and aversive motivational states, and may serve as a crucial circuit node for bidirectionally normalizing maladaptive behaviours.

Synaptic Dysfunction In the Hippocampus Accompanies Learning and Memory Deficits In Human Immunodeficiency Virus Type-1 Tat Transgenic Mice. Fitting S, Ignatowska-Jankowska BM, Bull C, Skoff RP, Lichtman AH, Wise LE, Fox MA, Su J, Medina AE, Krahe TE, Knapp PE, Guido W, Hauser KF. Biol Psychiatry. 2013 Mar 1; 73(5): 443-453.
Human immunodeficiency virus (HIV) associated neurocognitive disorders (HAND), including memory dysfunction, continue to be a major clinical manifestation of HIV type-1 infection. Viral proteins released by infected glia are thought to be the principal triggers of inflammation and bystander neuronal injury and death, thereby driving key symptomatology of HAND. The authors used a glial fibrillary acidic protein-driven, doxycycline-inducible HIV type-1 transactivator of transcription (Tat) transgenic mouse model and examined structure-function relationships in hippocampal pyramidal cornu ammonis 1 (CA1) neurons using

morphologic, electrophysiological (long-term potentiation [LTP]), and behavioral (Morris water maze, fear-conditioning) approaches. Tat induction caused a variety of different inclusions in astrocytes characteristic of lysosomes, autophagic vacuoles, and lamellar bodies, which were typically present within distal cytoplasmic processes. In pyramidal CA1 neurons, Tat induction reduced the number of apical dendritic spines, while disrupting the distribution of synaptic proteins (synaptotagmin 2 and gephyrin) associated with inhibitory transmission but with minimal dendritic pathology and no evidence of pyramidal neuron death. Electrophysiological assessment of excitatory postsynaptic field potential at Schaffer collateral/commissural fiber-CA1 synapses showed near total suppression of LTP in mice expressing Tat. The loss in LTP coincided with disruptions in learning and memory. Tat expression in the brain results in profound functional changes in synaptic physiology and in behavior that are accompanied by only modest structural changes and minimal pathology. The authors conclude that Tat likely contributes to HAND by causing molecular changes that disrupt synaptic organization, with inhibitory presynaptic terminals containing synaptotagmin 2 appearing especially vulnerable.

CRF Acts In the Midbrain To Attenuate Accumbens Dopamine Release To Rewards But Not Their Predictors. Wanat MJ, Bonci A, Phillips PE. Nat Neurosci. 2013 Apr; 16(4): 383-385. Stressors affect dopamine-dependent behaviors such as motivation, although the underlying neurobiological mechanism is not well defined. The authors report that corticotropin-releasing factor (CRF) acts in the ventral tegmental area (VTA) to reduce the motivation to work for food rewards. CRF in the VTA regulates dopamine output in a stimulus- and pathway-specific manner, offering a mechanism by which acute stress selectively regulates information transmission via the VTA to reprioritize motivated behavior.

Chemical Probes Of Endocannabinoid Metabolism. Blankman JL, Cravatt BF. Pharmacol Rev 2013; 65(2): 849-871.
The endocannabinoid signaling system regulates diverse physiologic processes and has attracted considerable attention as a potential pharmaceutical target for treating diseases, such as pain, anxiety/depression, and metabolic disorders. The principal ligands of the endocannabinoid system are the lipid transmitters N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), which activate the two major cannabinoid receptors, CB1 and CB2. Anandamide and 2-AG signaling pathways in the nervous system are terminated by enzymatic hydrolysis mediated primarily by the serine hydrolases fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. In this review, the authors discuss the development of FAAH and MAGL inhibitors and their pharmacological application to investigate the function of anandamide and 2-AG signaling pathways in preclinical models of neurobehavioral processes, such as pain, anxiety, and addiction. They place emphasis on how these studies are beginning to discern the different roles played by anandamide and 2-AG in the nervous system and the resulting implications for advancing endocannabinoid hydrolase inhibitors as next-generation therapeutics.

Determining Target Engagement In Living Systems. Simon GM, Niphakis MJ, Cravatt BF. Nat Chem Biol 2013; 9(4): 200-205.
Chemical probes are critical tools for elucidating the biological functions of proteins and can lead to new medicines for treating disease. The pharmacological validation of protein function

requires verification that chemical probes engage their intended targets *in vivo*. Here the authors discuss technologies, both established and emergent, for measuring target engagement in living systems and propose that determining this parameter should become standard practice for chemical probe and drug discovery programs.

Genome-Wide Association Study On Detailed Profiles Of Smoking Behavior and Nicotine Dependence In A Twin Sample. Loukola A, Wedenoja J, Keskitalo-Vuokko K, Broms U, Korhonen T, Ripatti S, Sarin A-P, Pitkaniemi J, He L, Happola A, Heikkila K, Chou Y-L, Pergadia ML, Heath AC, Montgomery GW, Martin NG, Madden PAF, Kaprio J. Mol Psychiatry 2013. Epub ahead of print.
Smoking is a major risk factor for several somatic diseases and is also emerging as a causal factor for neuropsychiatric disorders. Genome-wide association (GWA) and candidate gene studies for smoking behavior and nicotine dependence (ND) have disclosed too few predisposing variants to account for the high estimated heritability. Previous large-scale GWA studies have had very limited phenotypic definitions of relevance to smoking-related behavior, which has likely impeded the discovery of genetic effects. The authors performed GWA analyses on 1114 adult twins ascertained for ever smoking from the population-based Finnish Twin Cohort study. The availability of 17 smoking-related phenotypes allowed us to comprehensively portray the dimensions of smoking behavior, clustered into the domains of smoking initiation, amount smoked and ND. These results highlight a locus on 16p12.3, with several single-nucleotide polymorphisms (SNPs) in the vicinity of CLEC19A showing association (P<1 ýý 10(-6)) with smoking quantity. Interestingly, CLEC19A is located close to a previously reported attention-deficit hyperactivity disorder (ADHD) linkage locus and an evident link between ADHD and smoking has been established. Intriguing preliminary association (P<1 ýý 10(-5)) was detected between DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) ND diagnosis and several SNPs in ERBB4, coding for a Neuregulin receptor, on 2q33. The association between ERBB4 and DSM-IV ND diagnosis was replicated in an independent Australian sample. Recently, a significant increase in ErbB4 and Neuregulin 3 (Nrg3) expression was revealed following chronic nicotine exposure and withdrawal in mice and an association between NRG3 SNPs and smoking cessation success was detected in a clinical trial. ERBB4 has previously been associated with schizophrenia; further, it is located within an established schizophrenia linkage locus and within a linkage locus for a smoker phenotype identified in this sample. In conclusion, the authors disclose novel tentative evidence for the involvement of ERBB4 in ND, suggesting the involvement of the Neuregulin/ErbB signalling pathway in addictions and providing a plausible link between the high co-morbidity of schizophrenia and ND.

Human-specific Regulation of MeCP2 Levels In Fetal Brains by microRNA miR-483-5p. Han K, Gennarino VA, Lee Y, Pang K, Hashimoto-Torii K, Choufani S, Raju CS, Oldham MC, Weksberg R, Rakic P, Liu Z, Zoghbi HY. Genes Dev. 2013 Mar 1; 27: 485-490.
Proper neurological function in humans requires precise control of levels of the epigenetic regulator methyl CpG-binding protein 2 (MeCP2). MeCP2 protein levels are low in fetal brains, where the predominant MECP2 transcripts have an unusually long 3' untranslated region (UTR). Here, the authors show that miR-483-5p, an intragenic microRNA of the imprinted IGF2, regulates MeCP2 levels through a human-specific binding site in the MECP2 long 3' UTR. They demonstrate the inverse correlation of miR-483-5p and

MeCP2 levels in developing human brains and fibroblasts from Beckwith-Wiedemann syndrome patients. Importantly, expression of miR-483-5p rescues abnormal dendritic spine phenotype of neurons overexpressing human MeCP2. In addition, miR-483-5p modulates the levels of proteins of the MeCP2-interacting corepressor complexes, including HDAC4 and TBL1X. These data provide insight into the role of miR-483-5p in regulating the levels of MeCP2 and interacting proteins during human fetal development.

Stochastic Gene Expression In Mammals: Lessons From Olfaction. Magklara A, Lomvardas S.Trends Cell Biol. 2013 May 17. [Epub ahead of print].
One of the remarkable characteristics of higher organisms is the enormous assortment of cell types that emerge from a common genome. The immune system, with the daunting duty of detecting an astounding number of pathogens, and the nervous system with the equally bewildering task of perceiving and interpreting the external world, are the quintessence of cellular diversity. As we began to appreciate decades ago, achieving distinct expression programs among similar cell types cannot be accomplished solely by deterministic regulatory systems, but by the involvement of some type of stochasticity. In the last few years our understanding of these non-deterministic mechanisms is advancing, and this review will provide a brief summary of the current view of stochastic gene expression with focus on olfactory receptor (OR) gene choice, the epigenetic underpinnings of which recently began to emerge.

Translational Research In Nicotine Dependence. Turner JR, Gold A, Schnoll R, Blendy JA. Cold Spring Harb Perspect Med. 2013 Mar 1; 3(3): a012153.
Nicotine addiction accounts for 4.9 million deaths each year. Furthermore, although smoking represents a significant health burden in the United States, at present there are only three FDA-approved pharmacotherapies currently on the market: (1) nicotine replacement therapy, (2) bupropion, and (3) varenicline. Despite this obvious gap in the market, the complexity of nicotine addiction in addition to the increasing cost of drug development makes targeted drug development prohibitive. Furthermore, using combinations of mouse and human studies, additional treatments could be developed from off-the-shelf, currently approved medication lists. This article reviews translational studies targeting manipulations of the cholinergic system as a viable therapeutic target for nicotine addiction.

Psychostimulant-Induced Neuroadaptations In Nucleus Accumbens AMPA Receptor Transmission. Pierce RC, Wolf ME. Cold Spring Harb Perspect Med. 2013 Feb 1; 3(2): a012021. Medium spiny neurons of the nucleus accumbens serve as the interface between corticolimbic regions that elicit and modulate motivated behaviors, including those related to drugs of abuse, and motor regions responsible for their execution. Medium spiny neurons are excited primarily by AMPA-type glutamate receptors, making AMPA receptor transmission in the accumbens a key regulatory point for addictive behaviors. In animal models of cocaine addiction, changes in the strength of AMPA receptor transmission onto accumbens medium spiny neurons have been shown to underlie cocaine-induced behavioral adaptations related to cocaine seeking. Here the authors review changes in AMPA receptor levels and subunit composition that occur after discontinuing different types of cocaine exposure, as well as changes elicited by cocaine reexposure following abstinence or extinction. Signaling pathways

that regulate these cocaine-induced adaptations will also be considered, as they represent potential targets for addiction pharmacotherapies.

Systems Level Neuroplasticity In Drug Addiction. Feltenstein MW, See RE. Cold Spring Harb Perspect Med. 2013 May 1; 3(5): a011916.
Drug addiction is a chronic relapsing disorder for which research has been dedicated to understand the various factors that contribute to development, loss of control, and persistence of compulsive addictive behaviors. In this review, the authors provide a broad overview of various theories of addiction, drugs of abuse, and the neurobiology involved across the addiction cycle. Specific focus is devoted to the role of the mesolimbic pathway in acute drug reinforcement and occasional drug use, the mesocortical pathway and associated areas (e.g., the dorsal striatum) in escalation/ dependence, and the involvement of these pathways and associated circuits in mediating conditioned responses, drug craving, and loss of behavioral control thought to underlie withdrawal and relapse. With a better understanding of the neurobiological factors that underlie drug addiction, continued preclinical and clinical research will aid in the development of novel therapeutic interventions that can serve as effective long-term treatment strategies for drug-dependent individuals.

Epigenetics and Psychostimulant Addiction. Schmidt HD, McGinty JF, West AE, Sadri-Vakili G. Cold Spring Harb Perspect Med. 2013 Mar 1; 3(3): a012047.
Chronic drug exposure alters gene expression in the brain and produces long-term changes in neural networks that underlie compulsive drug taking and seeking. Exactly how drug-induced changes in synaptic plasticity and subsequent gene expression are translated into persistent neuroadaptations remains unclear. Emerging evidence suggests that complex drug-induced neuroadaptations in the brain are mediated by highly synchronized and dynamic patterns of gene regulation. Recently, it has become clear that epigenetic mechanisms contribute to drug-induced structural, synaptic, and behavioral plasticity by regulating expression of gene networks. Here the authors review how alterations in histone modifications, DNA methylation, and microRNAs regulate gene expression and contribute to psychostimulant addiction with a focus on the epigenetic mechanisms that regulate brain-derived neurotrophic factor (BDNF) expression following chronic cocaine exposure. Identifying epigenetic signatures that define psychostimulant addiction may lead to novel, efficacious treatments for drug craving and relapse.

Overinhibition Of Corticostriatal Activity Following Prenatal Cocaine Exposure. Wang W, Nitulescu I, Lewis JS, Lemos JC, Bamford IJ, Posielski NM, Storey GP, Phillips PE, Bamford NS. Ann Neurol. 2013 Mar; 73(3): 355-369.
Prenatal cocaine exposure (PCE) can cause persistent neuropsychological and motor abnormalities in affected children, but the physiological consequences of PCE remain unclear. Conclusions drawn from clinical studies can sometimes be confounded by polysubstance abuse and nutritional deprivation. However, existing observations suggest that cocaine exposure in utero, as in adults, increases synaptic dopamine and promotes enduring dopamine-dependent plasticity at striatal synapses, altering behaviors and basal ganglia function. The authors used a combination of behavioral measures, electrophysiology, optical imaging, and biochemical and electrochemical recordings to examine corticostriatal activity in adolescent mice exposed to cocaine in utero. They show that PCE caused abnormal dopamine-dependent

behaviors, including heightened excitation following stress and blunted locomotor augmentation after repeated treatment with amphetamine. These abnormal behaviors were consistent with abnormal γ-aminobutyric acid (GABA) interneuron function, which promoted a reversible depression in corticostriatal activity. PCE hyperpolarized and reduced tonic GABA currents in both fast-spiking and persistent low-threshold spiking type GABA interneurons to increase tonic inhibition at GABAB receptors on presynaptic corticostriatal terminals. Although D2 receptors paradoxically increased glutamate release following PCE, normal corticostriatal modulation by dopamine was reestablished with a GABAA receptor antagonist. The dynamic alterations at corticostriatal synapses that occur in response to PCE parallel the reported effects of repeated psychostimulants in mature animals, but differ in being specifically generated through GABAergic mechanisms. These results indicate approaches that normalize GABA and D2 receptor-dependent synaptic plasticity may be useful for treating the behavioral effects of PCE and other developmental disorders that are generated through abnormal GABAergic signaling.

Studying Task-Related Activity Of Individual Neurons In the Human Brain. Patel SR, Sheth SA, Martinez-Rubio C, Mian MK, Asaad WF, Gerrard JL, Kwon CS, Dougherty DD, Flaherty AW, Greenberg BD, Gale JT, Williams ZM, Eskandar EN. Nat Protoc. 2013 May; 8(5): 949-957. doi: 10.1038/nprot.2013.050. Epub 2013 Apr 18.
Single-neuronal studies remain the gold standard for studying brain function. Here the authors describe a protocol for studying task-related single-neuronal activity in human subjects during neurosurgical procedures involving microelectrode recordings. This protocol has two phases: a preoperative phase and an intraoperative phase. During the preoperative phase, the authors discuss informed consent, equipment setup and behavioral testing. During the intraoperative phase, they discuss the procedure for microelectrode recordings. Because patients are often awake during these procedures, this protocol can be performed in conjunction with behavioral tasks for studying a variety of cognitive functions. The authors describe the protocol in detail and provide two examples of expected results. In addition, they discuss the potential difficulties and pitfalls related to intraoperative studies. This protocol takes ~1.5 h to complete.

Immune Activation Of Human Brain Microvascular Endothelial Cells Inhibits HIV Replication In Macrophages. Li J, Wang Y, Wang X, Ye L, Zhou Y, Persidsky Y, Ho W. Blood. 2013 Apr 11; 121(15): 2934-2942.
There is limited information about the role of blood-brain barrier (BBB) endothelial cells (ECs) in the central nervous system (CNS) and their innate immunity against HIV. The authors examined whether brain ECs can be immunologically activated to produce antiviral factors that inhibit HIV replication in macrophages. Human brain microvascular ECs expressed functional toll-like receptor 3 (TLR3) that could be activated by polyinosinic-polycytidylic acid (PolyI:C), resulting in the induction of endogenous interferon-β (IFN-β) and IFN-λ. The TLR3 activation of ECs also induced the phosphorylation of interferon regulatory transcription factor 3 (IRF3) and IRF7, the key regulators of IFN signaling pathway. When supernatant (SN) of PolyI:C-activated EC cultures was applied to infected macrophage cultures, HIV replication was significantly suppressed. This SN action of ECs on HIV was mediated through both IFN-β and IFN-λ because antibodies to their receptors could neutralize the SN-mediated anti-HIV effect. The role of IFNs in EC-mediated anti-HIV activity is further supported by the

observation that treatment with SN from EC cultures induced the expression of IFN-stimulated genes (ISGs: ISG56, OAS-1, and MxA) in macrophages. These observations indicate that brain microvascular ECs may be a key regulatory bystander, playing a crucial role in the BBB innate immunity against HIV infection.

Cannabinoid- and Lysophosphatidylinositol-Sensitive Receptor GPR55 Boosts Neurotransmitter Release At Central Synapses. Sylantyev S, Jensen TP, Ross RA, Rusakov DA. Proc Natl Acad Sci U S A. 2013 Mar 26; 110(13): 5193-5198.
G protein-coupled receptor (GPR) 55 is sensitive to certain cannabinoids, it is expressed in the brain and, in cell cultures, it triggers mobilization of intracellular Ca(2+). However, the adaptive neurobiological significance of GPR55 remains unknown. Here, the authors use acute hippocampal slices and combine two-photon excitation Ca(2+) imaging in presynaptic axonal boutons with optical quantal analysis in postsynaptic dendritic spines to find that GPR55 activation transiently increases release probability at individual CA3-CA1 synapses. The underlying mechanism involves Ca(2+) release from presynaptic Ca(2+) stores, whereas postsynaptic stores (activated by spot-uncaging of inositol 1,4,5-trisphosphate) remain unaffected by GPR55 agonists. These effects are abolished by genetic deletion of GPR55 or by the GPR55 antagonist cannabidiol, a constituent of Cannabis sativa. GPR55 shows colocalization with synaptic vesicle protein vesicular glutamate transporter 1 in stratum radiatum. Short-term potentiation of CA3-CA1 transmission after a short train of stimuli reveals a presynaptic, Ca(2+) store-dependent component sensitive to cannabidiol. The underlying cascade involves synthesis of phospholipids, likely in the presynaptic cell, but not the endocannabinoids 2-arachidonoylglycerol or anandamide. These results thus unveil a signaling role for GPR55 in synaptic circuits of the brain.

Chloride Binding Site Of Neurotransmitter Sodium Symporters. Kantcheva AK, Quick M, Shi L, Winther AM, Stolzenberg S, Weinstein H, Javitch JA, Nissen P. Proc Natl Acad Sci U S A. 2013 May 21; 110(21): 8489-8494. doi: 10.1073/pnas.1221279110. Epub 2013 May 2.
Neurotransmitter:sodium symporters (NSSs) play a critical role in signaling by reuptake of neurotransmitters. Eukaryotic NSSs are chloride-dependent, whereas prokaryotic NSS homologs like LeuT are chloride-independent but contain an acidic residue (Glu290 in LeuT) at a site where eukaryotic NSSs have a serine. The LeuT-E290S mutant displays chloride-dependent activity. The authors show that, in LeuT-E290S cocrystallized with bromide or chloride, the anion is coordinated by side chain hydroxyls from Tyr47, Ser290, and Thr254 and the side chain amide of Gln250. The bound anion and the nearby sodium ion in the Na1 site organize a connection between their coordinating residues and the extracellular gate of LeuT through a continuous H-bond network. The specific insights from the structures, combined with results from substrate binding studies and molecular dynamics simulations, reveal an anion-dependent occlusion mechanism for NSS and shed light on the functional role of chloride binding.

Molecular Chaperoning Function Of Ric-8 Is To Fold Nascent Heterotrimeric G Protein α Subunits. Chan P, Thomas CJ, Sprang SR, Tall GG. Proc Natl Acad Sci U S A. 2013 Mar 5; 110(10): 3794-3799.
The authors have shown that resistance to inhibitors of cholinesterase 8 (Ric-8) proteins regulate an early step of heterotrimeric G protein α (Gα) subunit biosynthesis. Here,

mammalian and plant cell-free translation systems were used to study Ric-8A action during Gα subunit translation and protein folding. Gα translation rates and overall produced protein amounts were equivalent in mock and Ric-8A-immunodepleted rabbit reticulocyte lysate (RRL). GDP-AlF4(-)-bound Gαi, Gαq, Gα13, and Gαs produced in mock-depleted RRL had characteristic resistance to limited trypsinolysis, showing that these G proteins were folded properly. Gαi, Gαq, and Gα13, but not Gαs produced from Ric-8A-depleted RRL were not protected from trypsinization and therefore not folded correctly. Addition of recombinant Ric-8A to the Ric-8A-depleted RRL enhanced GDP-AlF4(-)-bound Gα subunit trypsin protection. Dramatic results were obtained in wheat germ extract (WGE) that has no endogenous Ric-8 component. WGE-translated Gαq was gel filtered and found to be an aggregate. Ric-8A supplementation of WGE allowed production of Gαq that gel filtered as a ~100 kDa Ric-8A:Gαq heterodimer. Addition of GTPγS to Ric-8A-supplemented WGE Gαq translation resulted in dissociation of the Ric-8A:Gαq heterodimer and production of functional Gαq-GTPγS monomer. Excess Gβγ supplementation of WGE did not support functional Gαq production. The molecular chaperoning function of Ric-8 is to participate in the folding of nascent G protein α subunits.

Subjective Costs Drive Overly Patient Foraging Strategies In Rats On An Intertemporal Foraging Task. Wikenheiser AM, Stephens DW, Redish AD. Proc Natl Acad Sci U S A. 2013 May 14; 110(20): 8308-8313.
Laboratory studies of decision making often take the form of two-alternative, forced-choice paradigms. In natural settings, however, many decision problems arise as stay/go choices. The authors designed a foraging task to test intertemporal decision making in rats via stay/go decisions. Subjects did not follow the rate-maximizing strategy of choosing only food items associated with short delays. Instead, rats were often willing to wait for surprisingly long periods, and consequently earned a lower rate of food intake than they might have by ignoring long-delay options. The authors tested whether foraging theory or delay discounting models predicted the behavior they observed but found that these models could not account for the strategies subjects selected. Subjects' behavior was well accounted for by a model that incorporated a cost for rejecting potential food items. Interestingly, subjects' cost sensitivity was proportional to environmental richness. These findings are at odds with traditional normative accounts of decision making but are consistent with retrospective considerations having a deleterious influence on decisions (as in the "sunk-cost" effect). More broadly, these findings highlight the utility of complementing existing assays of decision making with tasks that mimic more natural decision topologies.

Posttraining Optogenetic Manipulations Of Basolateral Amygdala Activity Modulate Consolidation Of Inhibitory Avoidance Memory In Rats. Huff ML, Miller RL, Deisseroth K, Moorman DE, LaLumiere RT. Proc Natl Acad Sci U S A. 2013 Feb 26; 110(9): 3597-3602.
Memory consolidation studies, including those examining the role of the basolateral amygdala (BLA), have traditionally used techniques limited in their temporal and spatial precision. The development of optogenetics provides increased precision in the control of neuronal activity that can be used to address the temporal nature of the modulation of memory consolidation. The present experiments, therefore, investigated whether optogenetically stimulating and inhibiting BLA activity immediately after training on an inhibitory avoidance task enhances and impairs retention, respectively. The BLA of male Sprague-Dawley rats was transduced to

express either ChR2(E123A) or archaerhodopsin-3 from the Halorubrum sodomense strain TP009 (ArchT). Immediately after inhibitory avoidance training, rats received optical stimulation or inhibition of the BLA, and 2 d later, rats' retention was tested. Stimulation of ChR2(E123A)-expressing neurons in the BLA using trains of 40-Hz light pulses enhanced retention, consistent with recording studies suggesting the importance of BLA activity at this frequency. Light pulses alone given to control rats had no effect on retention. Inhibition of ArchT-expressing neurons in the BLA for 15 min, but not 1 min, significantly impaired retention. Again, illumination alone given to control rats had no effect on retention, and BLA inhibition 3 h after training had no effect. These findings provide critical evidence of the importance of specific frequency patterns of activity in the BLA during consolidation and indicate that optogenetic manipulations can be used to alter activity after a learning event to investigate the processes underlying memory consolidation.

Computational Analysis Of Anti-HIV-1 Antibody Neutralization Panel Data To Identify Potential Functional Epitope Residues. West AP Jr, Scharf L, Horwitz J, Klein F, Nussenzweig MC, Bjorkman PJ. Proc Natl Acad Sci U S A. 2013 Jun 25; 110(26): 10598-10603.

Advances in single-cell antibody cloning methods have led to the identification of a variety of broadly neutralizing anti-HIV-1 antibodies. The authors developed a computational tool (Antibody Database) to help identify critical residues on the HIV-1 envelope protein whose natural variation affects antibody activity. Their simplifying assumption was that, for a given antibody, a significant portion of the dispersion of neutralization activity across a panel of HIV-1 strains is due to the amino acid identity or glycosylation state at a small number of specific sites, each acting independently. A model of an antibody's neutralization IC50 was developed in which each site contributes a term to the logarithm of the modeled IC50. The analysis program attempts to determine the set of rules that minimizes the sum of the residuals between observed and modeled IC50 values. The predictive quality of the identified rules may be assessed in part by whether there is support for rules within individual viral clades. As a test case, the authors analyzed antibody 8ANC195, an anti-glycoprotein gp120 antibody of unknown specificity. The model for this antibody indicated that several glycosylation sites were critical for neutralization. The authors evaluated this prediction by measuring neutralization potencies of 8ANC195 against HIV-1 in vitro and in an antibody therapy experiment in humanized mice. These experiments confirmed that 8ANC195 represents a distinct class of glycan-dependent anti-HIV-1 antibody and validated the utility of computational analysis of neutralization panel data.

Kelch-like 3 and Cullin 3 Regulate Electrolyte Homeostasis Via Ubiquitination and Degradation of WNK4. Shibata S, Zhang J, Puthumana J, Stone KL, Lifton RP. Proc Natl Acad Sci U S A. 2013 May 7; 110(19): 7838-7843.

Pseudohypoaldosteronism type II (PHAII) is a rare Mendelian syndrome featuring hypertension and hyperkalemia resulting from constitutive renal salt reabsorption and impaired K(+) secretion. Recently, mutations in Kelch-like 3 (KLHL3) and Cullin 3 (CUL3), components of an E3 ubiquitin ligase complex, were found to cause PHAII, suggesting that loss of this complex's ability to target specific substrates for ubiquitination leads to PHAII. By MS and coimmunoprecipitation, the authors show that KLHL3 normally binds to WNK1 and WNK4, members of WNK (with no lysine) kinase family that have previously been found

mutated in PHAII. The authors show that this binding leads to ubiquitination, including polyubiquitination, of at least 15 specific sites in WNK4, resulting in reduced WNK4 levels. Dominant disease-causing mutations in KLHL3 and WNK4 both impair WNK4 binding, ubiquitination, and degradation. WNK4 normally induces clearance of the renal outer medullary K(+) channel (ROMK) from the cell surface. The authors show that WT but not mutant KLHL3 inhibits WNK4-induced reduction of ROMK level. They show that PHAII-causing mutations in WNK4 lead to a marked increase in WNK4 protein levels in the kidney in vivo. These findings demonstrate that CUL3-RING (really interesting new gene) ligases that contain KLHL3 target ubiquitination of WNK4 and thereby regulate WNK4 levels, which in turn regulate levels of ROMK. These findings reveal a specific role of CUL3 and KLHL3 in electrolyte homeostasis and provide a molecular explanation for the effects of disease-causing mutations in both KLHL3 and WNK4.

A Strategy To Capture and Characterize the Synaptic Transcriptome. Puthanveettil SV, Antonov I, Kalachikov S, Rajasethupathy P, Choi YB, Kohn AB, Citarella M, Yu F, Karl KA, Kinet M, Morozova I, Russo JJ, Ju J, Moroz LL, Kandel ER. Proc Natl Acad Sci U S A. 2013 Apr 30; 110(18): 7464-7469.
Here the authors describe a strategy designed to identify RNAs that are actively transported to synapses during learning. Their approach is based on the characterization of RNA transport complexes carried by molecular motor kinesin. Using this strategy in Aplysia, the authors have identified 5,657 unique sequences consisting of both coding and noncoding RNAs from the CNS. Several of these RNAs have key roles in the maintenance of synaptic function and growth. One of these RNAs, myosin heavy chain, is critical in presynaptic sensory neurons for the establishment of long-term 4, but not for its persistence.

Amphetamine Actions At the Serotonin Transporter Rely On the Availability Of Phosphatidylinositol-4,5-Bisphosphate. Buchmayer F, Schicker K, Steinkellner T, Geier P, Stübiger G, Hamilton PJ, Jurik A, Stockner T, Yang JW, Montgomery T, Holy M, Hofmaier T, Kudlacek O, Matthies HJ, Ecker GF, Bochkov V, Galli A, Boehm S, Sitte HH. Proc Natl Acad Sci U S A. 2013 Jul 9; 110(28): 11642-11647.
Nerve functions require phosphatidylinositol-4,5-bisphosphate (PIP2) that binds to ion channels, thereby controlling their gating. Channel properties are also attributed to serotonin transporters (SERTs); however, SERT regulation by PIP2 has not been reported. SERTs control neurotransmission by removing serotonin from the extracellular space. An increase in extracellular serotonin results from transporter-mediated efflux triggered by amphetamine-like psychostimulants. Herein, the authors altered the abundance of PIP2 by activating phospholipase-C (PLC), using a scavenging peptide, and inhibiting PIP2-synthesis. They tested the effects of the verified scarcity of PIP2 on amphetamine-triggered SERT functions in human cells. They observed an interaction between SERT and PIP2 in pull-down assays. On decreased PIP2 availability, amphetamine-evoked currents were markedly reduced compared with controls, as was amphetamine-induced efflux. Signaling downstream of PLC was excluded as a cause for these effects. A reduction of substrate efflux due to PLC activation was also found with recombinant noradrenaline transporters and in rat hippocampal slices. Transmitter uptake was not affected by PIP2 reduction. Moreover, SERT was revealed to have a positively charged binding site for PIP2. Mutation of the latter resulted in a loss of amphetamine-induced SERT-mediated efflux and currents, as well as a lack of PIP2-dependent

effects. Substrate uptake and surface expression were comparable between mutant and WT SERTs. These findings demonstrate that PIP2 binding to monoamine transporters is a prerequisite for amphetamine actions without being a requirement for neurotransmitter uptake. These results open the way to target amphetamine-induced SERT-dependent actions independently of normal SERT function and thus to treat psychostimulant addiction.

Error Processing and Gender-Shared and -Specific Neural Predictors Of Relapse In Cocaine Dependence. Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CS. Brain. 2013 Apr; 136(Pt 4): 1231-1244.
Deficits in cognitive control are implicated in cocaine dependence. Previously, combining functional magnetic resonance imaging and a stop signal task, the authors demonstrated altered cognitive control in cocaine-dependent individuals. However, the clinical implications of these cross-sectional findings and, in particular, whether the changes were associated with relapse to drug use, were not clear. In a prospective study, the authors recruited 97 treatment-seeking individuals with cocaine dependence to perform the stop signal task during functional magnetic resonance imaging and participate in follow-up assessments for 3 months, during which time cocaine use was evaluated with timeline follow back and ascertained by urine toxicology tests. Functional magnetic resonance imaging data were analysed using general linear models as implemented in Statistical Parametric Mapping 8, with the contrast 'stop error greater than stop success trials' to index error processing. Using voxelwise analysis with logistic and Cox regressions, the authors identified brain activations of error processing that predict relapse and time to relapse. In females, decreased error-related activations of the thalamus and dorsal anterior cingulate cortex predicted relapse and an earlier time to relapse. In males, decreased error-related activations of the dorsal anterior cingulate cortex and left insula predicted relapse and an earlier time to relapse. These regional activations were validated with data resampling and predicted relapse with an average area under the curve of 0.849 in receiver operating characteristic analyses. These findings provide direct evidence linking deficits in cognitive control to clinical outcome in a moderate-sized cohort of cocaine-dependent individuals. These results may provide a useful basis for future studies to examine how psychosocial factors interact with cognitive control to determine drug use and to evaluate the efficacy of pharmacological or behavioural treatment in remediating deficits of cognitive control in cocaine addicts.

Brain Inositol Is A Novel Stimulator For Promoting Cryptococcus Penetration Of the Blood-Brain Barrier. Liu TB, Kim JC, Wang Y, Toffaletti DL, Eugenin E, Perfect JR, Kim KJ, Xue C. PLoS Pathog. 2013 Apr; 9(4): e1003247.
Cryptococcus neoformans is the most common cause of fungal meningitis, with high mortality and morbidity. The reason for the frequent occurrence of Cryptococcus infection in the central nervous system (CNS) is poorly understood. The facts that human and animal brains contain abundant inositol and that Cryptococcus has a sophisticated system for the acquisition of inositol from the environment suggests that host inositol utilization may contribute to the development of cryptococcal meningitis. In this study, the authors found that inositol plays an important role in Cryptococcus traversal across the blood-brain barrier (BBB) both in an in vitro human BBB model and in in vivo animal models. The capacity of inositol to stimulate BBB crossing was dependent upon fungal inositol transporters, indicated by a 70% reduction in transmigration efficiency in mutant strains lacking two major inositol transporters, Itr1a and

Itr3c. Upregulation of genes involved in the inositol catabolic pathway was evident in a microarray analysis following inositol treatment. In addition, inositol increased the production of hyaluronic acid in Cryptococcus cells, which is a ligand known to binding host CD44 receptor for their invasion. These studies suggest an inositol-dependent Cryptococcus traversal of the BBB, and support the authors' hypothesis that utilization of host-derived inositol by Cryptococcus contributes to CNS infection.

Phosphorylation of CDK9 at Ser175 Enhances HIV Transcription and is a Marker of Activated P-TEFb in CD4(+) T Lymphocytes. Mbonye UR, Gokulrangan G, Datt M, Dobrowolski C, Cooper M, Chance MR, Karn J. PLoS Pathog. 2013 May; 9(5): e1003338.
The HIV transactivator protein, Tat, enhances HIV transcription by recruiting P-TEFb from the inactive 7SK snRNP complex and directing it to proviral elongation complexes. To test the hypothesis that T-cell receptor (TCR) signaling induces critical post-translational modifications leading to enhanced interactions between P-TEFb and Tat, the authors employed affinity purification-tandem mass spectrometry to analyze P-TEFb. TCR or phorbal ester (PMA) signaling strongly induced phosphorylation of the CDK9 kinase at Ser175. Molecular modeling studies based on the Tat/P-TEFb X-ray structure suggested that pSer175 strengthens the intermolecular interactions between CDK9 and Tat. Mutations in Ser175 confirm that this residue could mediate critical interactions with Tat and with the bromodomain protein BRD4. The S175A mutation reduced CDK9 interactions with Tat by an average of 1.7-fold, but also completely blocked CDK9 association with BRD4. The phosphomimetic S175D mutation modestly enhanced Tat association with CDK9 while causing a 2-fold disruption in BRD4 association with CDK9. Since BRD4 is unable to compete for binding to CDK9 carrying S175A, expression of CDK9 carrying the S175A mutation in latently infected cells resulted in a robust Tat-dependent reactivation of the provirus. Similarly, the stable knockdown of BRD4 led to a strong enhancement of proviral expression. Immunoprecipitation experiments show that CDK9 phosphorylated at Ser175 is excluded from the 7SK RNP complex. Immunofluorescence and flow cytometry studies carried out using a phospho-Ser175-specific antibody demonstrated that Ser175 phosphorylation occurs during TCR activation of primary resting memory CD4+ T cells together with upregulation of the Cyclin T1 regulatory subunit of P-TEFb, and Thr186 phosphorylation of CDK9. The authors conclude that the phosphorylation of CDK9 at Ser175 plays a critical role in altering the competitive binding of Tat and BRD4 to P-TEFb and provides an informative molecular marker for the identification of the transcriptionally active form of P-TEFb.

IL-1β Production Through The NLRP3 Inflammasome By Hepatic Macrophages Links Hepatitis C Virus Infection With Liver Inflammation and Disease. Negash AA, Ramos HJ, Crochet N, Lau DT, Doehle B, Papic N, Delker DA, Jo J, Bertoletti A, Hagedorn CH, Gale M Jr. PLoS Pathog. 2013 Apr; 9(4): e1003330.
Chronic hepatitis C virus (HCV) infection is a leading cause of liver disease. Liver inflammation underlies infection-induced fibrosis, cirrhosis and liver cancer but the processes that promote hepatic inflammation by HCV are not defined. The authors provide a systems biology analysis with multiple lines of evidence to indicate that interleukin-1β (IL-1β) production by intrahepatic macrophages confers liver inflammation through HCV-induced inflammasome signaling. Chronic hepatitis C patients exhibited elevated levels of serum IL-1β compared to healthy controls. Immunohistochemical analysis of healthy control and chronic

hepatitis C liver sections revealed that Kupffer cells, resident hepatic macrophages, are the primary cellular source of hepatic IL-1β during HCV infection. Accordingly, the authors found that both blood monocyte-derived primary human macrophages, and Kupffer cells recovered from normal donor liver, produce IL-1β after HCV exposure. Using the THP-1 macrophage cell-culture model, they found that HCV drives a rapid but transient caspase-1 activation to stimulate IL-1β secretion. HCV can enter macrophages through non-CD81 mediated phagocytic uptake that is independent of productive infection. Viral RNA triggers MyD88-mediated TLR7 signaling to induce IL-1β mRNA expression. HCV uptake concomitantly induces a potassium efflux that activates the NLRP3 inflammasome for IL-1β processing and secretion. RNA sequencing analysis comparing THP1 cells and chronic hepatitis C patient liver demonstrates that viral engagement of the NLRP3 inflammasome stimulates IL-1β production to drive proinflammatory cytokine, chemokine, and immune-regulatory gene expression networks linked with HCV disease severity. These studies identify intrahepatic IL-1β production as a central feature of liver inflammation during HCV infection. Thus, strategies to suppress NLRP3 or IL-1β activity could offer therapeutic actions to reduce hepatic inflammation and mitigate disease.

Ion Selectivity and Gating Mechanisms Of FNT Channels. Waight AB, Czyzewski BK, Wang DN. Curr Opin Struct Biol. 2013 Jun 14. [Epub ahead of print].
The phospholipid bilayer has evolved to be a protective and selective barrier by which the cell maintains high concentrations of life sustaining organic and inorganic material. As gatekeepers responsible for an immense amount of bidirectional chemical traffic between the cytoplasm and extracellular milieu, ion channels have been studied in detail since their postulated existence nearly three-quarters of a century ago. Over the past fifteen years, we have begun to understand how selective permeability can be achieved for both cationic and anionic ions. Our mechanistic knowledge has expanded recently with studies of a large family of anion channels, the Formate Nitrite Transport (FNT) family. This family has proven amenable to structural studies at a resolution high enough to reveal intimate details of ion selectivity and gating. With five representative members having yielded a total of 15 crystal structures, this family represents one of the richest sources of structural information for anion channels.

Individual Variation In Resisting Temptation: Implications For Addiction. Saunders BT, Robinson TE. Neurosci Biobehav Rev. 2013 Feb 21. [Epub ahead of print].
When exposed to the sights, sounds, smells and/or places that have been associated with rewards, such as food or drugs, some individuals have difficulty resisting the temptation to seek out and consume them. Others have less difficulty restraining themselves. Thus, Pavlovian reward cues may motivate maladaptive patterns of behavior to a greater extent in some individuals than in others. We are just beginning to understand the factors underlying individual differences in the extent to which reward cues acquire powerful motivational properties, and therefore, the ability to act as incentive stimuli. Here the authors review converging evidence from studies in both human and non-human animals suggesting that a subset of individuals are more "cue reactive", in that certain reward cues are more likely to attract these individuals to them and motivate actions to get them. They suggest that those individuals for whom Pavlovian reward cues become especially powerful incentives may be more vulnerable to impulse control disorders, such as binge eating and addiction.

Recovering From Cocaine: Insights From Clinical and Preclinical Investigations. Hanlon CA, Beveridge TJ, Porrino LJ. Neurosci Biobehav Rev. 2013 Apr 27. [Epub ahead of print].
Cocaine remains one of the most addictive substances of abuse and one of the most difficult to treat. Although increasingly sophisticated experimental and technologic advancements in the last several decades have yielded a large body of clinical and preclinical knowledge on the direct effects of cocaine on the brain, we still have a relatively incomplete understanding of the neurobiological processes that occur when drug use is discontinued. The goal of this manuscript is to review both clinical and preclinical data related to abstinence from cocaine and discuss the complementary conclusions that emerge from these different levels of inquiry. This commentary will address observed alterations in neural function, neural structure, and neurotransmitter system regulation that are present in both animal models of cocaine abstinence and data from recovering clinical populations. Although these different levels of inquiry are often challenging to integrate, emerging data discussed in this commentary suggest that from a structural and functional perspective, the preservation of cortical function that is perhaps the most important biomarker associated with extended abstinence from cocaine.

Adjusting Behavior To Changing Environmental Demands With Development. Lourenco F, Casey BJ. Neurosci Biobehav Rev. 2013 Mar 18. [Epub ahead of print].
Plasticity refers to changes in the brain that enable an organism to adapt its behavior in the face of changing environmental demands. The evolutionary role of plasticity is to provide the cognitive flexibility to learn from experiences, to monitor the world based on learned predictions, and adjust actions when these predictions are violated. Both progressive (myelination) and regressive (synaptic pruning) brain changes support this type of adaptation. Experience-driven changes in neural connections underlie the ability to learn and update thoughts and behaviors throughout life. Many cognitive and behavioral indices exhibit nonlinear life-span trajectories, suggesting the existence of specific sensitive developmental periods of heightened plasticity. The authors propose that age-related differences in learning capabilities and behavioral performance reflect the distinct maturational timetable of subcortical learning systems and modulatory prefrontal regions. They focus specifically on the developmental transition of adolescence, during which individuals experience difficulty flexibly adjusting their behavior when confronted with unexpected and emotionally salient events. In this article, the authors review the findings illustrating this phenomenon and how they vary by individual.

Exercise As A Novel Treatment For Drug Addiction: A Neurobiological and Stage-Dependent Hypothesis. Lynch WJ, Peterson AB, Sanchez V, Abel J, Smith MA. Neurosci Biobehav Rev. 2013 Jun 24; 37(8): 1622-1644.
Physical activity, and specifically exercise, has been suggested as a potential treatment for drug addiction. In this review, the authors discuss clinical and preclinical evidence for the efficacy of exercise at different phases of the addiction process. Potential neurobiological mechanisms are also discussed focusing on interactions with dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. While exercise generally produces an efficacious response, certain exercise conditions may be either ineffective or lead to detrimental effects depending on the level/type/timing of exercise exposure, the stage of addiction, the drug involved, and the subject population. During drug use initiation and withdrawal, its efficacy may be related to its ability to facilitate dopaminergic transmission,

and once addiction develops, its efficacy may be related to its ability to normalize glutamatergic and dopaminergic signaling and reverse drug-induced changes in chromatin via epigenetic interactions with brain-derived neurotrophic factor (BDNF) in the reward pathway. The authors conclude with future directions, including the development of exercise-based interventions alone or as an adjunct to other strategies for treating drug addiction.

Effect Of Chronic Delivery Of the Toll-Like Receptor 4 Antagonist (+)-Naltrexone On Incubation Of Heroin Craving. Theberge FR, Li X, Kambhampati S, Pickens CL, St Laurent R, Bossert JM, Baumann MH, Hutchinson MR, Rice KC, Watkins LR, Shaham Y. Biol Psychiatry. 2013 Apr 15; 73(8): 729-737.

Recent evidence implicates toll-like receptor 4 (TLR4) in opioid analgesia, tolerance, conditioned place preference, and self-administration. Here, the authors determined the effect of the TLR4 antagonist (+)-naltrexone (a μ-opioid receptor inactive isomer) on the time-dependent increases in cue-induced heroin seeking after withdrawal (incubation of heroin craving). In an initial experiment, the authors trained rats for 9 hours per day to self-administer heroin (.1 mg/kg/infusion) for 9 days; lever presses were paired with a 5-second tone-light cue. They then assessed cue-induced heroin seeking in 30-minute extinction sessions on withdrawal day 1; immediately after testing, they surgically implanted rats with Alzet minipumps delivering (+)-naltrexone (0, 7.5, 15, 30 mg/kg/day, subcutaneous) for 14 days. They then tested the rats for incubated cue-induced heroin seeking in 3-hour extinction tests on withdrawal day 13. The authors found that chronic delivery of (+)-naltrexone via minipumps during the withdrawal phase decreased incubated cue-induced heroin seeking. In follow-up experiments, they found that acute injections of (+)-naltrexone immediately before withdrawal day 13 extinction tests had no effect on incubated cue-induced heroin seeking. Furthermore, chronic delivery of (+)-naltrexone (15 or 30 mg/kg/day) or acute systemic injections (15 or 30 mg/kg) had no effect on ongoing extended access heroin self-administration. Finally, in rats trained to self-administer methamphetamine (.1 mg/kg/infusion, 9 hours/day, 9 days), chronic delivery of (+)-naltrexone (30 mg/kg/day) during the withdrawal phase had no effect on incubated cue-induced methamphetamine seeking. The present results suggest a critical role of TLR4 in the development of incubation of heroin, but not methamphetamine, craving.

5-Lipoxygenase Activating Protein Reduction Ameliorates Cognitive Deficit, Synaptic Dysfunction, and Neuropathology in a Mouse Model of Alzheimer's Disease.
Giannopoulos PF, Chu J, Joshi YB, Sperow M, Li JG, Kirby LG, Praticò D. Biol Psychiatry. 2013 May 15. [Epub ahead of print].

5-lipoxygenase activating protein (FLAP) is abundantly present in the central nervous system. Although its function has been extensively interrogated in the context of peripheral inflammation, novel roles for this protein are emerging in the central nervous system. The objective of this study was to investigate the functional role that FLAP plays in a mouse model of Alzheimer's disease (AD) with plaques and tangles (i.e., 3xTg mice). By implementing a genetic knockout of FLAP and pharmacologic inhibition with a FLAP inhibitor (MK-591), the authors evaluated the effect on the AD-like neuropathology, cognition, and synaptic plasticity in the 3xTg mice. They show that reduction of FLAP leads to amelioration of cognition and memory along with the rescuing of synaptic dysfunction at an early age before the development of overt neuropathology. Genetic knockout and pharmacologic inhibition of FLAP also yielded an improvement in AD pathology through a reduction in Aβ via the γ-

secretase pathway and a decrease in tau phosphorylation through the cdk5 pathway. These studies identify a novel functional role for FLAP in regulating memory and synaptic plasticity. They establish this protein at the crossroad of multiple pathways that ultimately contribute to the development of the entire AD-like phenotype, making it a viable therapeutic target with disease-modifying capacity for the treatment of this disease.

Sweetened-Fat Intake Sensitizes Gamma-Aminobutyric Acid-Mediated Feeding Responses Elicited From the Nucleus Accumbens Shell. Newman S, Pascal L, Sadeghian K, Baldo BA. Biol Psychiatry. 2013 May 1; 73(9): 843-850. doi: 10.1016/j.biopsych.2012.11.027. Epub 2013 Jan 8.

There is much interest in exploring whether reward-driven feeding can produce druglike plasticity in the brain. The gamma-aminobutyric acid (GABA) system in the nucleus accumbens (Acb) shell, which modulates hypothalamic feeding systems, is well placed to "usurp" homeostatic control of feeding. Nevertheless, it is unknown whether feeding-induced neuroadaptations occur in this system. Separate groups of ad libitum-maintained rats were exposed to daily bouts of sweetened-fat intake, predator stress, or intra-Acb shell infusions of either d-amphetamine (2 or 10 μg) or the μ-opioid agonist D-[Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO, 2.5 μg), then challenged with intra-Acb shell infusion of the GABAA agonist, muscimol (10 ng). Exposure to sweetened fat robustly sensitized muscimol-induced feeding. Sensitization was present 1 week after cessation of the palatable feeding regimen but had abated by 2 weeks. Rats exposed to sweetened fat did not show an altered feeding response to food deprivation. Repeated intra-Acb shell infusions of DAMGO (2.5 μg) also sensitized intra-Acb shell muscimol-driven feeding. However, neither repeated intra-Acb shell d-amphetamine infusions (2 or 10 μg) nor intermittent exposure to an aversive stimulus (predator stress) altered sensitivity to muscimol. The authors conclude that palatable feeding engenders hypersensitivity of Acb shell GABA responses; this effect may involve feeding-induced release of opioid peptides. Heightened arousal, aversive experiences, or increased catecholamine transmission alone are insufficient to produce the effect, and a hunger-induced feeding drive is insufficient to reveal the effect. These findings reveal a novel type of food-induced neuroadaptation within the Acb; possible implications for understanding crossover effects between food reward and drug reward are discussed.

Increased Small Conductance Calcium-Activated Potassium Type 2 Channel-Mediated Negative Feedback on N-methyl-D-aspartate Receptors Impairs Synaptic Plasticity Following Context-Dependent Sensitization to Morphine. Fakira AK, Portugal GS, Carusillo B, Melyan Z, Morón JA. Biol Psychiatry. 2013 Jun 1. pii: S0006-3223(13)00405-8. doi: 10.1016/j.biopsych.2013.04.026. [Epub ahead of print].

Hippocampal long-term potentiation (LTP) is impaired following repeated morphine administration paired with a novel context. This procedure produces locomotor sensitization that can be abolished by blocking calcium (Ca^{2+})-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) in the hippocampus. However, the mechanisms underlying LTP impairment remain unclear. Here, the authors investigate the role of N-methyl-D-aspartate receptors (NMDARs), AMPARs, and small conductance Ca^{2+}-activated potassium type 2 (SK2) channels in LTP induction after context-dependent sensitization to morphine. Mice were treated with saline or escalating doses of morphine (5, 8, 10, and 15 mg/kg) every 12 hours in a locomotor activity chamber and a challenge dose of 5

mg/kg morphine was given 1 week later. After the challenge, the hippocampi were removed to assay phosphatase 2A (PP2A) activity, NMDAR, and SK2 channel synaptic expression or to perform electrophysiological recordings. Impaired hippocampal LTP, which accompanied morphine-induced context-dependent sensitization, could not be restored by blocking Ca^{2+}-permeable AMPARs. Context-dependent sensitization to morphine altered hippocampal NMDAR subunit composition and enhanced the SK2 channel-mediated negative feedback on NMDAR. Increased PP2A activity observed following context-dependent sensitization suggests that the potentiated SK2 channel effect on NMDAR was mediated by increased SK2 sensitivity to Ca^{2+}. Finally, inhibition of SK2 channel or PP2A activity restored LTP. studies demonstrate that the SK2 channel-NMDAR feedback loop plays a role in opiate-induced impairment of hippocampal plasticity and that the positive modulation of SK2 channels occurs via increases in PP2A activity. This provides further evidence that small conductance Ca^{2+}-activated potassium channels play a role in drug-induced plasticity.

How Might Circadian Rhythms Control Mood? Let Me Count the Ways..... McClung CA. Biol Psychiatry. 2013 Apr 1. [Epub ahead of print].

Mood disorders are serious diseases that affect a large portion of the population. There have been many hypotheses put forth over the years to explain the development of major depression, bipolar disorder, and other mood disorders. These hypotheses include disruptions in monoamine transmission, hypothalamus-pituitary-adrenal axis function, immune function, neurogenesis, mitochondrial dysfunction, and neuropeptide signaling (to name a few). Nearly all people suffering from mood disorders have significant disruptions in circadian rhythms and the sleep/wake cycle. In fact, altered sleep patterns are one of the major diagnostic criteria for these disorders. Moreover, environmental disruptions to circadian rhythms, including shift work, travel across time zones, and irregular social schedules, tend to precipitate or exacerbate mood-related episodes. Recent studies have found that molecular clocks are found throughout the brain and body where they participate in the regulation of most physiological processes, including those thought to be involved in mood regulation. This review will summarize recent data that implicate the circadian system as a vital regulator of a variety of systems that are thought to play a role in the development of mood disorders.

Neural Correlates Of Stress- and Food Cue-Induced Food Craving In Obesity: Association With Insulin Levels. Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN. Diabetes Care. 2013 Feb; 36(2): 394-402.

Obesity is associated with alterations in corticolimbic-striatal brain regions involved in food motivation and reward. Stress and the presence of food cues may each motivate eating and engage corticolimibic-striatal neurocircuitry. It is unknown how these factors interact to influence brain responses and whether these interactions are influenced by obesity, insulin levels, and insulin sensitivity. The authors hypothesized that obese individuals would show greater responses in corticolimbic-striatal neurocircuitry after exposure to stress and food cues and that brain activations would correlate with subjective food craving, insulin levels, and HOMA-IR. Fasting insulin levels were assessed in obese and lean subjects who were exposed to individualized stress and favorite-food cues during functional MRI. Obese, but not lean, individuals exhibited increased activation in striatal, insular, and hypothalamic regions during exposure to favorite-food and stress cues. In obese but not lean individuals, food craving, insulin, and HOMA-IR levels correlated positively with neural activity in corticolimbic-striatal

brain regions during favorite-food and stress cues. The relationship between insulin resistance and food craving in obese individuals was mediated by activity in motivation-reward regions including the striatum, insula, and thalamus. These findings demonstrate that obese, but not lean, individuals exhibit increased corticolimbic-striatal activation in response to favorite-food and stress cues and that these brain responses mediate the relationship between HOMA-IR and food craving. Improving insulin sensitivity and in turn reducing corticolimbic-striatal reactivity to food cues and stress may diminish food craving and affect eating behavior in obesity.

Pain after Discontinuation of Morphine Treatment Is Associated with Synaptic Increase of GluA4-Containing AMPAR in the Dorsal Horn of the Spinal Cord. Cabañero D, Baker A, Zhou S, Hargett GL, Irie T, Xia Y, Beaudry H, Gendron L, Melyan Z, Carlton SM, Morón JA. Neuropsychopharmacology. 2013 Jul; 38(8): 1472-1484.
Withdrawal from prescribed opioids results in increased pain sensitivity, which prolongs the treatment. This pain sensitivity is attributed to neuroplastic changes that converge at the spinal cord dorsal horn. The authors have recently reported that repeated morphine administration triggers an insertion of GluA2-lacking (Ca(2+)-permeable) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR) in the hippocampus. This finding together with the reported involvement of AMPAR in the mechanisms underlying inflammatory pain led the authors to hypothesize a role for spinal AMPAR in opioid-induced pain behavior. Mice treated with escalating doses of morphine showed hypersensitivity to mechanical stimulation. Intrathecal administration of a Ca(2+)-permeable AMPAR selective blocker disrupted morphine-induced mechanical sensitivity. Analysis of the expression and phosphorylation levels of AMPAR subunits (GluA1/2/3/4) in homogenates and in postsynaptic density fractions from spinal cord dorsal horns showed an increase in GluA4 expression and phosphorylation in the postsynaptic density after morphine. Co-immunoprecipitation analyses suggested an increase in GluA4 homomers (Ca(2+)-permeable AMPAR) and immunohistochemical staining localized the increase in GluA4 levels in laminae III-V. The excitatory postsynaptic currents (EPSCs) recorded in laminae III-V showed enhanced sensitivity to Ca(2+)-permeable AMPAR blockers in morphine-treated mice. Furthermore, current-voltage relationships of AMPAR-mediated EPSCs showed that rectification index (an indicator of Ca(2+)-permeable AMPAR contribution) is increased in morphine-treated but not in saline-treated mice. These effects could be reversed by infusion of GluA4 antibody through patch pipette. This is the first direct evidence for a role of GluA4-containing AMPAR in morphine-induced pain and highlights spinal GluA4-containing AMPAR as targets to prevent the morphine-induced pain sensitivity.

Extracellular Signal-Regulated Kinase In the Basolateral Amygdala, But Not the Nucleus Accumbens Core, Is Critical For Context-Response-Cocaine Memory Reconsolidation In Rats. Wells AM, Arguello AA, Xie X, Blanton MA, Lasseter HC, Reittinger AM, Fuchs RA. Neuropsychopharmacology. 2013 Apr; 38(5): 753-762.
The reconsolidation of cocaine memories following retrieval is necessary for the sustained ability of a cocaine-paired environmental context to elicit cocaine seeking. Extracellular signal-regulated kinase (ERK) is an intracellular signaling molecule involved in nucleus accumbens core (NACc)-mediated reconsolidation of Pavlovian cocaine memories. Here, the authors used a rodent model of drug context-elicited relapse to test the hypothesis that ERK

would be similarly required for the reconsolidation of context-response-cocaine memories that underlie drug context-induced reinstatement of instrumental cocaine-seeking behavior, with a focus on the NACc and on the basolateral amygdala (BLA), another important locus for the reconsolidation of cocaine memories. The authors show that the mitogen-activated protein kinase (MEK)/ERK1/2 inhibitor, U0126 (1.0 μg/0.5 μl/hemisphere), microinfused bilaterally into the BLA--but not the NACc--immediately after brief re-exposure to a previously cocaine-paired context (that is, cocaine-memory reactivation), significantly attenuated subsequent drug context-induced cocaine seeking relative to vehicle (VEH). This effect in the BLA was associated with a transient inhibition of ERK1/2 phosphorylation, and it depended on memory reactivation given that U0126 administered following exposure to a novel context did not alter subsequent cocaine seeking. Furthermore, similar to U0126, baclofen+muscimol-induced (B+M; 106.8/5.7 ng/0.5 μl/hemisphere) neural inactivation of the NACc, following cocaine-memory reactivation, failed to alter subsequent cocaine seeking. These findings demonstrate that ERK activation in the BLA, but not the NACc, is required for the reconsolidation of context-response-cocaine associative memories. Together with prior research, these results suggest that contextual drug-memory reconsolidation in Pavlovian and instrumental settings involves distinct neuroanatomical mechanisms.

Temporal Pattern of Cocaine Intake Determines Tolerance vs Sensitization of Cocaine Effects at the Dopamine Transporter. Calipari ES, Ferris MJ, Zimmer BA, Roberts DC, Jones SR. Neuropsychopharmacology. 2013 Jun 19. doi: 10.1038/npp.2013.136. [Epub ahead of print].

The dopamine transporter (DAT) is responsible for terminating dopamine (DA) signaling and is the primary site of cocaine's reinforcing actions. Cocaine self-administration has been shown previously to result in changes in cocaine potency at the DAT. To determine whether the DAT changes associated with self-administration are due to differences in intake levels or temporal patterns of cocaine-induced DAT inhibition, the authors manipulated cocaine access to produce either continuous or intermittent elevations in cocaine brain levels. Long-access (LgA, 6h) and short-access (ShA, 2h) continuous self-administration produced similar temporal profiles of cocaine intake that were sustained throughout the session; however, LgA had greater intake. ShA and intermittent-access (IntA, 6h) produced the same intake, but different temporal profiles, with 'spiking' brain levels in IntA compared with constant levels in ShA. IntA consisted of 5-min access periods alternating with 25-min timeouts, which resulted in bursts of high responding followed by periods of no responding. DA release and uptake, as well as the potency of cocaine for DAT inhibition, were assessed by voltammetry in the nucleus accumbens slices following control, IntA, ShA, and LgA self-administration. Continuous-access protocols (LgA and ShA) did not change DA parameters, but the 'spiking' protocol (IntA) increased both release and uptake of DA. In addition, high continuous intake (LgA) produced tolerance to cocaine, while 'spiking' (IntA) produced sensitization, relative to ShA and naive controls. Thus, intake and pattern can both influence cocaine potency, and tolerance seems to be produced by high intake, while sensitization is produced by intermittent temporal patterns of intake.

The Volitional Nature Of Nicotine Exposure Alters Anandamide and Oleoylethanolamide Levels In the Ventral Tegmental Area. Buczynski MW, Polis IY, Parsons LH. Neuropsychopharmacology. 2013 Mar; 38(4): 574-584. doi: 10.1038/npp.2012.210.

Cannabinoid-1 receptors (CB(1)) have an important role in nicotine reward and their function is disrupted by chronic nicotine exposure, suggesting nicotine-induced alterations in endocannabinoid (eCB) signaling. However, the effects of nicotine on brain eCB levels have not been rigorously evaluated. Volitional intake of nicotine produces physiological and behavioral effects distinct from forced drug administration, although the mechanisms underlying these effects are not known. This study compared the effects of volitional nicotine self-administration (SA) and forced nicotine exposure (yoked administration (YA)) on levels of eCBs and related neuroactive lipids in the ventral tegmental area (VTA) and other brain regions. Brain lipid levels were indexed both by in vivo microdialysis in the VTA and lipid extractions from brain tissues. Nicotine SA, but not YA, reduced baseline VTA dialysate oleoylethanolamide (OEA) levels relative to nicotine-naïve controls, and increased anandamide (AEA) release during nicotine intake. In contrast, all nicotine exposure paradigms increased VTA dialysate 2-arachidonoyl glycerol (2-AG) levels. Thus, nicotine differentially modulates brain lipid (2-AG, AEA, and OEA) signaling, and these modulations are influenced by the volitional nature of the drug exposure. Corresponding bulk tissue analysis failed to identify these lipid changes. Nicotine exposure had no effect on fatty acid amide hydrolase activity in the VTA, suggesting that changes in AEA and OEA signaling result from alterations in their nicotine-induced biosynthesis. Both CB(1) (by AEA and 2-AG) and non-CB(1) (by OEA) targets can alter the excitability and activity of the dopaminergic neurons in the VTA. Collectively, these findings implicate disrupted lipid signaling in the motivational effects of nicotine.

A Gαs DREADD Mouse For Selective Modulation Of cAMP Production In Striatopallidal Neurons. Farrell MS, Pei Y, Wan Y, Yadav PN, Daigle TL, Urban DJ, Lee HM, Sciaky N, Simmons A, Nonneman RJ, Huang XP, Hufeisen SJ, Guettier JM, Moy SS, Wess J, Caron MG, Calakos N, Roth BL. Neuropsychopharmacology. 2013 Apr; 38(5): 854-862.

Here, the authors describe a newly generated transgenic mouse in which the Gs DREADD (rM3Ds), an engineered G protein-coupled receptor, is selectively expressed in striatopallidal medium spiny neurons (MSNs). They first show that in vitro, rM3Ds can couple to Gαolf and induce cAMP accumulation in cultured neurons and HEK-T cells. The rM3Ds was then selectively and stably expressed in striatopallidal neurons by creating a transgenic mouse in which an adenosine2A (adora2a) receptor-containing bacterial artificial chromosome was employed to drive rM3Ds expression. In the adora2A-rM3Ds mouse, activation of rM3Ds by clozapine-N-oxide (CNO) induces DARPP-32 phosphorylation, consistent with the known consequence of activation of endogenous striatal Gαs-coupled GPCRs. They then tested whether CNO administration would produce behavioral responses associated with striatopallidal Gs signaling and in this regard CNO dose-dependently decreases spontaneous locomotor activity and inhibits novelty induced locomotor activity. Last, we show that CNO prevented behavioral sensitization to amphetamine and increased AMPAR/NMDAR ratios in transgene-expressing neurons of the nucleus accumbens shell. These studies demonstrate the utility of adora2a-rM3Ds transgenic mice for the selective and noninvasive modulation of Gαs

signaling in specific neuronal populations in vivo.This unique tool provides a new resource for elucidating the roles of striatopallidal MSN Gαs signaling in other neurobehavioral contexts.

Different Adaptations in AMPA Receptor Transmission in the Nucleus Accumbens after Short vs Long Access Cocaine Self-Administration Regimens. Purgianto A, Scheyer AF, Loweth JA, Ford KA, Tseng KY, Wolf ME. Neuropsychopharmacology. 2013 Aug; 38(9): 1789-1797.

Ca(2+)-permeable AMPA receptors (CP-AMPARs) accumulate in the nucleus accumbens (NAc) after -1 month of withdrawal from a long-access cocaine self-administration regimen (6h/d, 10d). This is functionally significant because CP-AMPARs mediate the 'incubated' cue-induced cocaine craving produced by this regimen. The authors' present goal was to determine if other commonly employed cocaine self-administration regimens also elicit CP-AMPAR accumulation. They compared four regimens, named according to whether sessions were short-access (ShA, 2h) or long-access (LgA, 6h) and the total number of sessions: LgA/10d (already shown to elicit CP-AMPAR accumulation), ShA/11d, ShA/20-24d, and LgA/20-24d. In the latter regimens, rats began with 10 days of ShA and then entered a differential phase (10-14 days) in which ShA sessions either continued or switched to LgA. Controls self-administered saline. After >40 days of withdrawal, whole-cell patch-clamp recordings were performed in NAc core medium spiny neurons to assess the contribution of CP-AMPAR transmission, based on the magnitude of synaptic suppression elicited by bath application of the selective CP-AMPAR antagonist naspm (100μM). Naspm produced a non-significant (-10%) attenuation of electrically evoked local excitatory postsynaptic current in the saline and ShA groups. By contrast, a significant naspm-induced synaptic attenuation (25-30%) was observed in both the LgA groups. Further analyses indicate that this emergence of CP-AMPAR transmission in the LgA groups is associated with increased baseline responsiveness of MSN to excitatory drive. Together with data on cocaine infusions in each group, these results show that CP-AMPAR accumulation and enhanced glutamate transmission is associated with longer sessions (6h), rather than the number of sessions or cocaine infusions.

Chronic Interferon-α Decreases Dopamine 2 Receptor Binding and Striatal Dopamine Release in Association with Anhedonia-Like Behavior in Nonhuman Primates. Felger JC, Mun J, Kimmel HL, Nye JA, Drake DF, Hernandez CR, Freeman AA, Rye DB, Goodman MM, Howell LL, Miller AH. Neuropsychopharmacology. 2013 May 9. [Epub ahead of print].

Neuroimaging studies in humans have demonstrated that inflammatory cytokines target basal ganglia function and presynaptic dopamine (DA), leading to symptoms of depression. Cytokine-treated nonhuman primates also exhibit evidence of altered DA metabolism in association with depressive-like behaviors. To further examine cytokine effects on striatal DA function, eight rhesus monkeys (four male, four female) were administered interferon (IFN)-α (20MIU/m^2 s.c.) or saline for 4 weeks. In vivo microdialysis was used to investigate IFN-α effects on DA release in the striatum. In addition, positron emission tomography (PET) with [^{11}C]raclopride was used to examine IFN-α-induced changes in DA2 receptor (D2R) binding potential before and after intravenous amphetamine administration. DA transporter binding was measured by PET using [^{18}F]2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)nortropane. Anhedonia-like behavior (sucrose consumption) was assessed during saline and IFN-α administration. In vivo microdialysis demonstrated decreased release of DA after 4 weeks of IFN-α administration compared with saline. PET neuroimaging also revealed

decreased DA release after 4 weeks of IFN-α as evidenced by reduced displacement of [^{11}C]raclopride following amphetamine administration. In addition, 4 weeks of IFN-α was associated with decreased D2R binding but no change in the DA transporter. Sucrose consumption was reduced during IFN-α administration and was correlated with decreased DA release at 4 weeks as measured by in vivo microdialysis. Taken together, these findings indicate that chronic peripheral IFN-α exposure reduces striatal DA release in association with anhedonia-like behavior in nonhuman primates. Future studies examining the mechanisms of cytokine effects on DA release and potential therapeutic strategies to reverse these changes are warranted.

Dual Inhibition Of Endocannabinoid Catabolic Enzymes Produces Enhanced Antiwithdrawal Effects In Morphine-Dependent Mice. Ramesh D, Gamage TF, Vanuytsel T, Owens RA, Abdullah RA, Niphakis MJ, Shea-Donohue T, Cravatt BF, Lichtman AH. Neuropsychopharma-cology. 2013 May; 38(6): 1039-1049.

Inhibition of the endocannabinoid catabolic enzymes, monoacylglycerol lipase (MAGL) or fatty acid amide hydrolase (FAAH) attenuates naloxone-precipitated opioid withdrawal signs in mice via activation of CB1 receptors. Complete FAAH inhibition blocks only a subset of withdrawal signs, whereas complete MAGL inhibition elicits enhanced antiwithdrawal efficacy, but is accompanied with some cannabimimetic side effects. Thus, the primary objective of the present study was to determine whether combined, full FAAH inhibition and partial MAGL represents an optimal strategy to reduce opioid withdrawal. To test this hypothesis, the authors examined whether combined administration of high-dose of the FAAH inhibitor PF-3845 and low-dose of the MAGL inhibitor JZL184, as well as the novel dual FAAH-MAGL inhibitor SA-57, which is 100-fold more potent in inhibiting FAAH than MAGL, would prevent spontaneous withdrawal in morphine-dependent mice, a model with greater face validity than precipitating withdrawal with μ-opioid receptor antagonists. Strikingly, a combination of low-dose JZL184 and high-dose PF-3845 as well as the dual inhibitor SA-57 reduced all abrupt withdrawal signs (ie, platform jumping, paw flutters, head shakes, diarrhea, and total body weight loss), but did not elicit any cannabimimetic side effects. In addition, JZL184 or PF-3845 blocked naloxone-precipitated hypersecretion in morphine-dependent small intestinal tissue. Collectively, these results are the first to show that endocannabinoid catabolic enzyme inhibitors reduce abrupt withdrawal in morpine-dependent mice and are effective in a novel in vitro model of opioid withdrawal. More generally, these findings support the idea that joint MAGL and FAAH inhibition represents a promising approach for the treatment of opioid dependence.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

White Matter Alterations at 33-Year Follow-Up in Adults with Childhood Attention-Deficit/Hyperactivity Disorder. Cortese S, Imperati D, Zhou J, Proal E, Klein RG, Mannuzza S, Ramos-Olazagasti MA, Milham MP, Kelly C, Castellanos FX. Biol Psychiatry. 2013 Apr 5. [Epub ahead of print].

Attention-deficit/hyperactivity disorder (ADHD) is increasingly conceived as reflecting altered functional and structural brain connectivity. The latter can be addressed with diffusion tensor imaging (DTI). The authors examined fractional anisotropy (FA), a DTI index related to white matter structural properties, in adult male subjects diagnosed with ADHD in childhood (probands) and matched control subjects without childhood ADHD. Additionally, they contrasted FA among probands with and without current ADHD in adulthood and control subjects. Participants were from an original cohort of 207 boys and 178 male control subjects. At 33-year follow-up, analyzable DTI scans were obtained in 51 probands (41.3±2.8 yrs) and 66 control subjects (41.2±3.1 yrs). Voxel-based FA was computed with tract-based spatial statistics, controlling for multiple comparisons. Probands with childhood ADHD exhibited significantly lower FA than control subjects without childhood ADHD in the right superior and posterior corona radiata, right superior longitudinal fasciculus, and in a left cluster including the posterior thalamic radiation, the retrolenticular part of the internal capsule, and the sagittal stratum ($p<.05$, corrected). Fractional anisotropy was significantly decreased relative to control subjects in several tracts in both probands with current and remitted ADHD, who did not differ significantly from each other. Fractional anisotropy was not significantly increased in probands in any region. Decreased FA in adults with childhood ADHD regardless of current ADHD might be an enduring trait of ADHD. White matter tracts with decreased FA connect regions involved in high-level as well as sensorimotor functions, suggesting that both types of processes are involved in the pathophysiology of ADHD.

Physiological Regulation at 9 Months of Age in Infants Prenatally Exposed to Cigarettes. Schuetze P, Eiden RD, Colder CR, Gray TR, Huestis MA. Infancy. 013; 18(2): 233-255.

The primary purpose of this study was to examine the association between prenatal cigarette exposure and physiological regulation at 9 months of age. Specifically, the authors explored the possibility that any association between prenatal cigarette exposure and infant physiological regulation was moderated by postnatal environmental tobacco smoke (ETS) exposure or infant gender. The authors evaluated whether male infants with prenatal cigarette exposure or infants who were also exposed to ETS after birth had the highest levels of physiological dysregulation. Respiratory sinus arrhythmia (RSA) was obtained from 206 (142 exposed and 64 nonexposed) infants during a baseline period and during procedures designed to elicit both positive and negative affect. There was a significant suppression of RSA during the negative affect task for nonexposed infants but not for exposed infants. Postnatal ETS exposure did not moderate this association; however, gender did moderate this association such that boys with prenatal cigarette exposure had a significant increase in RSA rather than the suppression seen among both nonexposed boys and girls. These results provide additional support for the idea that boys are particularly vulnerable to the effects of prenatal cigarette exposure.

Changes in Smoking Patterns During Pregnancy. Eiden RD, Homish GG, Colder CR, Schuetze P, Gray TR, Huestis MA. Subst Use Misuse. 2013 May; 48(7): 513-522.
This study examined trajectories of smoking during pregnancy among low-income smokers and differences on demographics, psychopathology, and smoking outcome expectancies among women with different smoking trajectories. The sample consisted of 215 urban pregnant smokers living in the United States. Results indicated four trajectories of smoking and significant changes over time within each trajectory. Persistent smokers had the highest demographic and mental health risks, reported higher craving compared to light smokers, and were more likely to endorse smoking to reduce negative affect, for state enhancement motives. Implications for intervention are discussed.

Prenatal Cocaine Exposure Alters Functional Activation in the Ventral Prefrontal Cortex and its Structural Connectivity with the Amygdala. Li Z, Santhanam P, Coles CD, Ellen Lynch M, Hamann S, Peltier S, Hu X. Psychiatry Res. 2013 Jul 30; 213(1): 47-55.
Prenatal cocaine exposure (PCE) is associated with arousal dysregulation, and alterations of amygdala activity in response to emotional arousal have previously been reported. However, voluntary regulation of emotional affect, enabling appropriate neural response to different streams of stimuli, must also engage prefrontal regions, yet the impact of PCE on these prefrontal mechanisms has not been investigated. Recent neuroimaging studies have shown the involvement of ventral prefrontal cortex (vPFC) in the modulation of amygdala reactivity and the mediation of effective emotional regulation. Based on these findings, using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), the present study compared functional activations of the vPFC as well as its structural connectivity with the amygdala between groups of PCE and control adolescents. In a working memory task with emotional distracters, the PCE adolescents exhibited less capability of increasing their vPFC activation in response to increased memory load, which corresponded with their less suppressed amygdala activation. Reduced structural connectivity between the vPFC and the amygdala was also observed from DTI measurement in the PCE group. In addition, correlations between amygdala activation and (i) vPFC activation, as well as (ii) amygdala-vPFC structural connectivity, were observed in the control but not in the PCE group. These data complement previous findings of the impact of PCE on the activity of the amygdala and extend our understanding of the neurobiological mechanisms underlying the effect of PCE on arousal dysregulation reported in human and animal studies.

Selective Impact of Early Parental Responsivity on Adolescent Stress Reactivity. Hackman DA, Betancourt LM, Brodsky NL, Kobrin L, Hurt H, Farah MJ. PLoS One. 2013; 8(3): e58250. doi: 10.1371/journal.pone.0058250. 2013 Mar 13. [Epub ahead of print].
Research in animals has shown that early life experience, particularly parenting behaviors, influences later-life stress reactivity. Despite the tremendous relevance of this finding to human development and brain function, it has not been tested prospectively in humans. In this study two aspects of parenting were measured at age 4 in a sample of healthy, low socioeconomic status, African American children, and stress reactivity was measured in the same children 11-14 years later using a modified version of the Trier Social Stress Test (n = 55). Salivary cortisol was measured before, during and after the stressor and data were analyzed using piecewise hierarchical linear modeling. Parental responsivity, independent of the use of physical discipline, was positively related to cortisol reactivity. Effects were

independent of subjective appraisals of the stressor and were also independent of other environmental risk factors and current psychosocial functioning. Therefore, this study demonstrates in a novel and precise fashion that early childhood parental responsivity prospectively and independently predicts stress reactivity in adolescence.

Prospective Effects of Adolescent Indicators of Behavioral Disinhibition on DSM-IV Alcohol, Tobacco, and Illicit Drug Dependence in Young Adulthood. Palmer RH, Knopik VS, Rhee SH, Hopfer CJ, Corley RC, Young SE, Stallings MC, Hewitt JK. Addict Behav. 2013 Sep; 38(9): 2415-2421.
The objective of this study was to identify robust predictors of drug dependence. This longitudinal study included 2,361 male and female twins from an ongoing longitudinal study at the Center for Antisocial Drug Dependence (CADD) at the University of Colorado Boulder and Denver campuses. Twins were recruited for the CADD project while they were between the ages of 12 and 18. Participants in the current study were on average approximately 15 years of age during the first wave of assessment and approximately 20 years of age at the second wave of assessment. The average time between assessments was five years. A structured interview was administered at each assessment to determine patterns of substance use and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; Fourth Edition) attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and drug dependence symptoms. Cloninger's Tridimensional Personality Questionnaire was also used to assess novelty seeking tendencies (NS). At the second wave of assessment, DSM-IV dependence symptoms were reassessed using the same interview. Path analyses were used to examine direct and indirect mechanisms linking psychopathology and drug outcomes. Adolescent substance use, CD, and NS predicted young adult substance dependence, whereas the predictive effects of ADHD were few and inconsistent. Furthermore, CD and NS effects were partially mediated by adolescent substance use. Adolescent conduct problems, novelty seeking, and drug use are important indices of future drug problems. The strongest predictor was novelty seeking.

A Preliminary Experimental Investigation of Peer Influence on Risk-Taking among Adolescent Smokers and Non-Smokers. Cavalca E, Kong G, Liss T, Reynolds EK, Schepis TS, Lejuez CW, Krishnan-Sarin S. Drug Alcohol Depend. 2013 Apr 1; 129(1-2): 163-166.
Epidemiological evidence suggests that peer influence plays a significant role in a variety of adolescent risk-taking behaviors, including tobacco use. The authors attempted to establish this relationship in a controlled laboratory setting. They modified the Balloon Analog Risk Task (BART) task to include a peer component to investigate whether peer influences alter risk-taking behaviors. Thirty-nine adolescents (22 smokers, 17 non-smokers) completed one experimental session during which the standard and peer BART were presented in counterbalanced order, with the dependent measures being adjusted mean number of pumps and explosions. The authors also examined the relationship of changes in the BART (standard-peer) to personality measures of impulsivity (BIS-11) and resistance to peer influence (RPI). A significant interaction of BART type and smoking status was present (p=.05); specifically smokers had a greater increase in the number of explosions by 2.27 (SD=3.12) compared to an increase of .29 (SD=2.87) by non-smokers. BIS-11 scores were related to peer-influenced BART changes: those who were more impulsive experienced greater changes in risk-taking, but no similar relationships were observed for the RPI. These results suggest that peer

influences enhance risk-taking among adolescents, and that smokers may be more susceptible to these influences.

Influence of Social Stress on Risk-Taking Behavior in Adolescents. Reynolds EK, Schreiber WM, Geisel K, Macpherson L, Ernst M, Lejuez CW. J Anxiety Disord. 2013 Apr; 27(3): 272-277.
Risk-taking behavior involves making choices with uncertain positive or negative outcomes. Evidence suggests that risk-taking behavior is influenced by emotional state. One such emotional experience is social anxiety, which has been related to both risk-avoidant and risk-seeking decision making. The present study examined a community sample of 34 adolescents grouped into low (Low SA Group) and high (High SA Group) social anxiety (SA). Both groups were compared on changes in performance on a risk taking task (Balloon Analogue Risk Task) between a social threat condition (modified Trier Social Stress Test, High Stress) and a control condition (Low Stress). These conditions were administered on different days, and the order was counterbalanced across subjects. A group×condition interaction revealed that the High SA Group showed greater risk-taking behavior when exposed to the High Stress Condition compared to the Low Stress Condition, while the Low SA Group evidenced no difference between the two conditions. Interpretations for the increased risk behavior under the condition of social stress for those high in social anxiety are discussed as well as implications for understanding the complex relationship between social anxiety and risk behavior.

Cortisol Reactivity in Two-Year-Old Children Prenatally Exposed to Methamphetamine. Kirlic N, Newman E, Lagasse LL, Derauf C, Shah R, Smith LM, Arria AM, Huestis MA, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Abar B, Neal CR, Lester BM. J Stud Alcohol Drugs. 2013 May; 74(3): 447-451.
Until now, the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in children with prenatal methamphetamine exposure (PME) had been unexamined. Previous research indicates that prenatal exposure to stimulant drugs is associated with dose-response alterations in neural growth and connectivity and consequent neurobehavioral deficits. In addition, children of drug-using parents are at an increased risk for exposure to chronic postnatal stress. In this preliminary study, the authors examined the associations of PME and postnatal environmental stress with cortisol stress reactivity in children with PME. Participants were 2-year-old children (N = 123; 55.3% male) with PME from a multicenter longitudinal Infant, Development, Environment, and Lifestyle Study. Saliva samples were obtained before and after a stress-inducing separation task. Hierarchical multiple regression analyses examined prenatal drug exposure, methodological and postnatal stress covariates, and interactions between levels of PME and postnatal stress. Mild to moderate potential for child physical abuse moderated increased cortisol reactivity in high exposed children with PME. Blunted cortisol reactivity was associated with caregiver's postnatal alcohol use, child's behavioral dysregulation, and the interaction between higher levels of PME and caregiver's psychopathology. Consistent with the known effects of stimulant drugs and chronically stressful environments on the HPA axis and, thus, the toxic stress and allostatic load phenomena, these results imply that elevated PME may be associated with alterations in the programming of the HPA axis reflecting hyperactivity, which under significant and chronic environmental stress then may become hypoactive.

Prenatal Tobacco Exposure Predicts Differential Brain Function during Working Memory in Early Adolescence: A Preliminary Investigation. Bennett DS, Mohamed FB, Carmody DP, Malik M, Faro SH, Lewis M. Brain Imaging Behav. 2013 Mar; 7(1): 49-59.
Children prenatally exposed to tobacco exhibit higher rates of learning and emotional-behavioral problems related to worse working memory performance. Brain function, however, among tobacco exposed children while performing a working memory task has not previously been examined. This study compared the brain function of tobacco-exposed (n=7) and unexposed (n=11) 12-year-olds during a number N-back working memory task using an event-related functional magnetic resonance imaging (fMRI) design. Prenatal alcohol exposure, neonatal medical problems, environmental risk, and sex were statistically controlled. Tobacco-exposed children showed greater activation in inferior parietal regions, whereas unexposed children showed greater activation in inferior frontal regions. These differences were observed in the context of correct responses, suggesting that exposed and unexposed children use different brain regions and approaches to succeed in working memory tasks. Implications for future research and intervention are discussed.

Externalizing Problems in Late Childhood as a Function of Prenatal Cocaine Exposure and Environmental Risk. Bennett DS, Marini VA, Berzenski SR, Carmody DP, Lewis M. J Pediatr Psychol. 2013 Apr; 38(3): 296-308.
The objective of this study was to examine whether prenatal cocaine exposure (PCE) predicts externalizing problems in late childhood. Externalizing problems were assessed using caregiver, teacher, and child ratings and a laboratory task when children (N = 179; 74 cocaine exposed) were aged 8-10 years. PCE, environmental risk, sex, neonatal health, other prenatal exposures, and foster care history were examined as predictors of externalizing problems. Multiple regression analyses indicated that PCE, environmental risk, and male sex explained significant variance in externalizing problems in late childhood. Models varied by source of information. PCE predicted externalizing problems for child laboratory behavior and interacted with sex because males with PCE reported more externalizing problems. PCE did not predict caregiver or teacher ratings of externalizing problems. The effect of PCE on externalizing problems may persist into late childhood. The findings highlight the potential importance of including child-based measures of externalizing problems in studies of prenatal exposure.

Parenting Styles and Emotional Intelligence of HIV-Affected Children in Thailand. Lee SJ, Li L, Thammawijaya P. AIDS Care. 2013 May 7. [Epub ahead of print].
The purpose of this study was to examine the impact of parenting styles on emotional intelligence of HIV-affected children in Thailand. This study uses data from 205 HIV-affected children in northern and northeastern Thailand. Correlation and regression analyses were used to examine the predictors of emotional intelligence. Children reporting higher levels of stress reported less caring parenting style (standardized beta [B]=-0.18, p=0.050). Children with higher self-esteem were also more likely to perceive their parents as caring (B=0.48, p=0.002). Children who scored lower on their self-esteem reported their parents to be more overprotective (B=-0.30, p=0.030), and children reporting higher levels of stress reported their parents to be more overprotective (B=0.12, p=0.010). Children reporting caring parenting style were significantly more likely to report higher emotional intelligence (B=0.66, p=0.001). Parenting styles play an important role in the emotional intelligence. Identifying and testing

interventions to help parents improve their parenting styles, while helping their HIV-affected children cope with stress and self-esteem, are essential in promoting mental health of HIV-affected children in Thailand.

Mental Health Disorders among Caregivers of Preschool Children in the Asenze Study in KwaZulu-Natal, South Africa. Chhagan MK, Mellins CA, Kauchali S, Craib MH, Taylor M, Kvalsvig JD, Davidson LL. Matern Child Health J. 2013 Mar 7. [Epub ahead of print]. Given the existing evidence linking parental depression with infant and early child development, the authors' aim was to describe the burden of mental health disorders among caregivers of young children aged 4-6 years living in an environment of poverty and high HIV seroprevalence. The authors employed baseline data from an epidemiologic study of the health and psychosocial needs of preschool-aged children. Primary caregivers of index children recruited from a household survey were screened for common mental disorders using the Client Diagnostic Questionnaire (CDQ). Sociodemographic, HIV and general health surveys were also conducted. Many caregivers (449/1,434; 31.3 %) screened positive for at least one psychiatric disorder on the CDQ, with post-traumatic-stress-disorder being the most common. Caregivers who screened positive for any disorder were more likely to be older, to have no individual sources of income and to have less formal education. Presence of a disorder was also significantly associated with lower employment levels within the household and death of a young child within the household. Known HIV-infected caregivers were more likely to have any mood disorder than caregivers who previously tested negative. The data support the need for mental health treatment interventions in South Africa, particularly interventions directed at PTSD and depression, and that take into account the high burden of poverty, HIV and childhood mortality. Given the limited formal mental health structure in South Africa to address these highly prevalent disorders; community-based mental health supports, available through decentralized health systems many be critical to delivering accessible interventions.

Effects of Prenatal and Postnatal Parent Depressive Symptoms on Adopted Child HPA Regulation: Independent and Moderated Influences. Laurent HK, Leve LD, Neiderhiser JM, Natsuaki MN, Shaw DS, Harold GT, Reiss D. Dev Psychol. 2013 May; 49(5): 876-886. This study used a prospective adoption design to investigate effects of prenatal and postnatal parent depressive symptom exposure on child hypothalamic-pituitary-adrenal (HPA) activity and associated internalizing symptoms. Birth mother prenatal symptoms and adoptive mother/father postnatal (9-month, 27-month) symptoms were assessed with the Beck Depression Inventory in a sample of 192 families as part of the Early Growth and Development adoption Study. Child morning/evening cortisol levels and child symptoms of internalizing disorders (according to mother/father report on the Child Behavior Checklist) were assessed at 54 months, and birth mother diurnal cortisol was measured at 48 months postnatal. Hierarchical linear modeling was used to test main effects and interactions of parents' symptoms predicting child cortisol, controlling for birth mother cortisol. Prenatal exposure to birth mother symptoms predicted lower child cortisol (main effect), as did postnatal exposure to adoptive parent symptoms (interaction effects). Adoptive mother 9-month symptoms exacerbated cortisol-lowering effects of both concurrent paternal symptoms and later (27-month) maternal symptoms, and the effect of birth mother cortisol. Lower child cortisol, in turn, was associated with higher child internalizing symptoms. Implications are discussed with respect to the intergenerational transmission of depression risk.

Dissociable Attentional and Affective Circuits in Medication-Naïve Children with Attention-Deficit/Hyperactivity Disorder. Posner J, Rauh V, Gruber A, Gat I, Wang Z, Peterson BS. Psychiatry Res. 2013 Jul 30; 213(1): 24-30.
Current neurocognitive models of attention-deficit/hyperactivity disorder (ADHD) suggest that neural circuits involving both attentional and affective processing make independent contributions to the phenomenology of the disorder. However, a clear dissociation of attentional and affective circuits and their behavioral correlates has yet to be shown in medication-naïve children with ADHD. Using resting-state functional connectivity MRI (rs-fcMRI) in a cohort of medication naïve children with (N=22) and without (N=20) ADHD, the authors demonstrate that children with ADHD have reduced connectivity in two neural circuits: one underlying executive attention (EA) and the other emotional regulation (ER). The authors also demonstrate a double dissociation between these two neural circuits and their behavioral correlates such that reduced connectivity in the EA circuit correlates with executive attention deficits but not with emotional lability, while on the other hand, reduced connectivity in the ER circuit correlates with emotional lability but not with executive attention deficits. These findings suggest potential avenues for future research such as examining treatment effects on these two neural circuits as well as the potential prognostic and developmental significance of disturbances in one circuit vs the other.

Prenatal Tobacco Exposure, Biomarkers for Tobacco in Meconium, and Neonatal Growth Outcomes. Himes SK, Stroud LR, Scheidweiler KB, Niaura RS, Huestis MA.. J Pediatr. 2013 May; 162(5): 970-975.
The objective of this study was to assess relationships between marker concentrations of tobacco in meconium and weekly self-reported maternal cigarette consumption, and prediction of neonatal growth outcomes. Pregnant mothers (n = 119) from a longitudinal maternal smoking and infant neurobehavioral study (Behavior and Mood in Babies and Mothers [BAM BAM]) provided daily tobacco smoking histories. Nicotine, cotinine, and trans-3'-hydroxycotinine concentrations were quantified in 111 neonatal meconium specimens by liquid chromatography-tandem mass spectrometry. Median self-reported third trimester smoking was 5.9 cigarettes per day among smokers. Meconium samples from infants born to non-smokers (n = 42) were negative for tobacco markers, while specimens from self-reported smokers (n = 41) were positive for (median, range) nicotine (50.1 ng/g, 3.9-294), cotinine (73.9 ng/g, 6.4-329), and trans-3'-hydroxycotinine (124.5 ng/g, 10.2-478). Quitters (n = 28) self-reported stopping smoking at gestational weeks 2-39. Four meconium specimens from quitters were positive for tobacco biomarkers. Reduced birth weight, length, and head circumference significantly correlated with presence of meconium markers but not with individual or total marker concentrations. Among quitters and smokers, reduced infant birth weight, head circumference, and gestational age correlated with total and average daily cigarette consumption in the second and third trimesters. Smoking cessation or reduction during pregnancy improved neonatal outcomes. The window of detection for tobacco in meconium appears to be the third trimester; however, low exposure in this trimester failed to be detected. These results will aid physicians in educating women who are pregnant or thinking about becoming pregnant on the negative consequences of smoking during pregnancy. In addition, infants at risk can be identified at birth to assist early intervention efforts.

Qualitative Change in Executive Control during Childhood and Adulthood. Chevalier N, Huber KL, Wiebe SA, Espy KA. Cognition. 2013 Jul; 128(1): 1-12.
Executive control development typically has been conceptualized to result from quantitative changes in the efficiency of the underlying processes. In contrast, the present study addressed the possibility of qualitative change with age by examining how children and adults detect task switches. Participants in three age groups (5- and 10-year-old children, young adults) completed two conditions of a cued task-switching paradigm where task cues were presented either in isolation or in conjunction with transition cues. Five-year-olds performed better with transition cues, whereas the reverse effect was observed at age 10 and with adults. Unlike 5-year-olds who detect switches after semantically processing cues, older participants strategically detect switches based on perceptual processing only. Age-related qualitative changes promote increasingly optimal adjustment of executive resources with age.

Parenting Practices in Pregnancy Smokers Compared to Non Smokers. Tandon M, Si X, Belden A, Spitznagel E, Wakschlag LS, Luby J. J Clin Med Res. 2013 Apr; 5(2): 84-91.
The present investigation compared parenting practices in a sample of preschoolers whose mothers reported smoking during pregnancy versus those who did not. A sample of n = 216, 3.0- to 5.11-year-old children, participants in an ongoing longitudinal study, was separated into those reportedly exposed to smoking in utero and those who were not. Parenting practices were compared between the two groups, using T-tests and exact logistic regressions. Multiple linear regressions and multivariate logistic regressions were used to examine the association between smoking status and parenting, controlling for variables also known to be associated with parenting practices. The current study findings suggest that smoking during pregnancy is associated with harsh parenting practices. The study results highlight the possible role of parenting in disruptive outcomes well-known in toddlers exposed to nicotine in utero and have implications for targeting early interventions in these populations.

Medication-taking Self-Efficacy and Medication Adherence among HIV-Infected Cocaine Users. Waldrop-Valverde D, Dong C, Ownby RL. J Assoc Nurses AIDS Care. 2013 May-Jun; 24(3): 198-206.
This prospective, observational study tested the ability of self-efficacy for taking antiretroviral medications to predict medication adherence among current and former cocaine and heroin users. Electronic monitors to record bottle openings and self-report measures of medication adherence were used. The sample included 99 men and women who were interviewed at 4-week intervals for 6 months. Mixed effects regression models to test the relationship of substance use and self-efficacy for medication-taking with percent of self-report adherence, dose adherence, number of days adherent, and adherence to medication schedule at each study visit showed that medication-taking self-efficacy was significantly related to all measures of adherence except schedule adherence. Findings also showed that electronically monitored adherence measures declined over the study period whereas self-report adherence did not. Findings suggest that self-efficacy can have a sustained effect on adherence to doses but may not be an influential predictor of adherence to their correct timing.

Adolescent Girls' ADHD Symptoms and Young Adult Driving: The Role of Perceived Deviant Peer Affiliation. Cardoos SL, Loya F, Hinshaw SP. J Clin Child Adolesc Psychol. 2013; 42(2): 232-242.

The authors' goal was to examine the role of adolescent perceived deviant peer affiliation in mediating or moderating the association between adolescent attention-deficit/hyperactivity disorder (ADHD) symptoms and young adult driving risk in females with and without ADHD. The overall sample included 228 ethnically and socioeconomically diverse girls with or without a diagnosis of ADHD in childhood (Wave 1; 6-12 years) followed through adolescence (Wave 2; 11-18 years) and into young adulthood (Wave 3; 17-24 years). A subsample of 103 girls with a driving license by Wave 3 and with full data for all study variables was utilized in this investigation. In adolescence, mothers and teachers reported on ADHD symptoms (inattention and hyperactivity/impulsivity), and participants reported on perceived deviant peer affiliation. In young adulthood, participants reported on driving behavior and outcomes, including number of accidents, number of moving vehicle citations, and ever having driven illegally. Covariates included age and adolescent oppositional defiant disorder/conduct disorder. Inattention directly predicted citations. Perceived deviant peer affiliation mediated the association between inattention and (a) accidents and (b) citations. In addition, perceived deviant peer affiliation moderated the association between hyperactivity/ impulsivity and accidents, with hyperactivity/impulsivity predicting accidents only for those with low perceived deviant peer affiliation. Perceived deviant peer affiliation appears to play an important role in the association between ADHD symptoms and driving outcomes. These findings provide preliminary evidence that both ADHD symptoms and peer processes should be targeted in interventions that aim to prevent negative driving outcomes in young women with and without ADHD.

Poverty, Problem Behavior, and Promise: Differential Susceptibility among Infants Reared in Poverty. Conradt E, Measelle J, Ablow JC. Psychol Sci. 2013 Mar 1; 24(3): 235-242.

Do infants reared in poverty exhibit certain physiological traits that make them susceptible to the positive and negative features of their caregiving environment? Guided by theories of differential susceptibility and biological sensitivity to context, the authors evaluated whether high baseline respiratory sinus arrhythmia (RSA) operates as a susceptibility factor among infants reared in poverty (N = 73). Baseline RSA at 5 months, the quality of the attachment relationship at 17 months, and the interaction of these two factors were included in their models as predictors of problem behavior at 17 months. Consistent with theory, results showed no significant differences in problem behavior among infants with low baseline RSA; however, infants with high baseline RSA exhibited the lowest levels of problem behavior if reared in an environment that fostered security, and they exhibited the highest levels of problem behavior if reared in an environment that fostered disorganization. These results have important implications for the psychological health of infants living in poverty.

Serotonin Transporter Gene Moderates Associations between Mood, Memory and Hippocampal Volume. Price JS, Strong J, Eliassen J, McQueeny T, Miller M, Padula CB, Shear P, Lisdahl K. Behav Brain Res. 2013 Apr 1; 242: 158-165.

The short (S) allele of the serotonin transporter gene (5-HTTLPR) is associated with reduced serotonin turnover compared to the long (L) allele in Caucasians. Few studies have examined

its impact on memory and brain structure in healthy young adults. Participants included 51 healthy young adults (25 female; ages 18-25). Multiple regressions examined the independent contribution of 5-HTTLPR biomarker genotype and its interactions with gender and sub-clinical depressive symptoms on hippocampal volumes and memory. The 5-HTTLPR genotype significantly interacted with gender in predicting larger left hippocampal volumes in S-carrying females and smaller hippocampal volumes in males ($p<.03$). Gender also moderated the impact of the 5-HTTLPR on neurocognition. In females, S allele carriers had poorer visual recall compared to L carriers ($p<.05$). A three-way interaction between 5-HTTLPR, gender, and depressive symptoms was also observed ($p<.04$). In females, larger left hippocampal volumes were associated with increased depressive symptoms while the opposite was seen in males. Finally, in male and female S carriers, increased depressive symptoms were marginally associated with poorer verbal memory ($p<.09$). In females, the 5-HTTLPR S allele was associated with poorer memory performance, increased depressive symptoms and larger hippocampal volumes. In males, the S allele predicted smaller hippocampal volumes and increased depressive symptoms. The opposite morphometric patterns likely reflect gender differences in adolescent hippocampal development. Larger longitudinal studies are needed to examine whether the impact of 5-HTTLPR genotype on neurocognition across development differs according to extent of mood symptoms and gender.

Cigar, Cigarillo, and Little Cigar Use among Current Cigarette-Smoking Adolescents. Schuster RM, Hertel AW, Mermelstein R. Nicotine Tob Res. 2013 May; 15(5): 925-931. Cigar, cigarillo, and little cigar (CCLC) use is prevalent among adolescents, particularly among those who smoke cigarettes. Using data from a longitudinal study of smoking patterns among adolescents, the authors examined differences between CCLC users (ever and past 30 days) and nonusers (never and not in the past 30 days) among adolescents who smoked a cigarette in the last month (n = 486). In our sample, 76.7% reported ever trying CCLC and 40.7% reported past month CCLC use. Bivariate analyses showed that CCLC users differed from nonusers in terms of demographics, other forms of tobacco use, other substance use, and mental health. Multivariate logistic regression analyses found that both ever and past 30-day CCLC use were strongly associated with being male and concurrent use of hookah. Ever CCLC use was also strongly associated with recent use of alcohol, and past 30-day CCLC use was strongly associated with antisocial behavior. After controlling for the number of days on which cigarettes were smoked in the past 30 days, past 30-day CCLC use was associated with most other forms of tobacco use, other substance use, and mental health, but not with number of cigarettes smoked in the past month and nicotine dependence. Results suggest that CCLC use is high among adolescent cigarette users and is associated with a variety of negative correlates. Importantly, many of these relationships are not accounted for by the adolescent's level of cigarette use. Further characterizing CCLC use will be important for developing more targeted and tailored interventions.

Discrepancies between Parent and Adolescent Beliefs about Daily Life Topics and Performance on an Emotion Recognition Task. De Los Reyes A, Lerner MD, Thomas SA, Daruwala S, Goepel K. Abnorm Child Psychol. 2013 Mar 17. [Epub ahead of print]. Parents and children and adolescents commonly disagree in their perceptions of a variety of behaviors, including the family relationship and environment, and child and adolescent psychopathology. To this end, numerous studies have examined to what extent increased

discrepant perceptions-particularly with regard to perceptions of the family relationship and environment-predict increased child and adolescent psychopathology. Parents' and children and adolescents' abilities to decode and identify others' emotions (i.e., emotion recognition) may play a role in the link between discrepant perceptions and child and adolescent psychopathology. The authors examined parents' and adolescents' emotion recognition abilities in relation to discrepancies between parent and adolescent perceptions of daily life topics. In a sample of 50 parents and adolescents ages 14-to-17 years (M = 15.4 years, 20 males, 54 % African-American), parents and adolescents were each administered a widely used performance-based measure of emotion recognition. Parents and adolescents were also administered a structured interview designed to directly assess each of their perceptions of the extent to which discrepancies existed in their beliefs about daily life topics (e.g., whether adolescents should complete their homework and carry out household chores). Interestingly, lower parent and adolescent emotion recognition performance significantly related to greater parent and adolescent perceived discrepant beliefs about daily life topics. The authors observed this relation whilst accounting for adolescent age and gender and levels of parent-adolescent conflict. These findings have important implications for understanding and using informant discrepancies in both basic developmental psychopathology research and applied research in clinic settings (e.g., discrepant views on therapeutic goals).

Opioid Receptor Polymorphism A118G Associated with Clinical Severity in a Drug Overdose Population. Manini AF, Jacobs MM, Vlahov D, Hurd YL. J Med Toxicol. 2013 Jun; 9(2): 148-154.

Genetic variations in the human mu-opioid receptor gene (OPRM1) mediate individual differences in response to pain and opiate addiction. The authors studied whether the common A118G (rs1799971) mu-opioid receptor single nucleotide polymorphism (SNP) was associated with overdose severity in humans. In addition, they examined an SNP responsible for alternative splicing of OPRM1 (rs2075572). They assessed allele frequencies of the above SNPs and associations with clinical severity in patients presenting to the emergency department (ED) with acute drug overdose. This work was designed as an observational cohort study over a 12-month period at an urban teaching hospital. Participants consisted of consecutive adult ED patients with suspected acute drug overdose for whom discarded blood samples were available for analysis. Specimens were linked with clinical variables (demographics, urine toxicology screens, clinical outcomes) then deidentified prior to genetic SNP analysis. Blinded genotyping was performed after standard DNA purification and whole genome amplification. In-hospital severe outcomes were defined as either respiratory arrest (RA; defined by mechanical ventilation) or cardiac arrest (CA; defined by loss of pulse). The authors analyzed 179 patients (61% male, median age 32) who overall suffered 15 RAs and four CAs, of whom three died. The 118G allele conferred 5.3-fold increased odds of CA/RA ($p<0.05$), while the rs2075572 variant allele was not associated with CA/RA. The 118G variant allele in the OPRM1 gene is associated with worse clinical severity in patients with acute drug overdose. These findings mark the first time that the 118G variant allele is linked with clinical drug overdose vulnerability.

Dynamic of Change in Pathological Personality Trait Dimensions: A Latent Change Analysis Among at-Risk Women. Barbot B, Hunter SR, Grigorenko EL, Luthar SS. J Psychopathol Behav Assess. 2013 Jun 1; 35(2): 173-185.
This study explores longitudinally a four-factor structure of pathological personality trait dimensions (PPTDs) to examine both its structural stability and intra-individual changes among PPTDs over time. Personality Disorder (PD) scales of the Millon Clinical Multiaxial Inventory-III were administered to 361 low-income women with various psychiatric conditions (drug dependence, depression), who were followed in a two-wave study over 5-years. Cross-sectional and longitudinal factor analyses outlined a robust factorial structure of PPTDs, extrinsically invariant over time, representing Negative Emotionality, Introversion, Antagonism and Impulsivity. Despite moderate rank-order stability in the PPTDs, results also indicated substantial intra-individual variability in the degree and direction of change, consistent with trajectories of change in participants' clinical diagnoses. Results are discussed in light of current debates on the structure and dynamic of pathological personality.

Effects of Prenatal and Postnatal Parent Depressive Symptoms on Adopted Child HPA Regulation: Independent and Moderated Influences. Laurent HK, Leve LD, Neiderhiser JM, Natsuaki MN, Shaw DS, Harold GT, Reiss D. Dev Psychol. 2013 May; 49(5): 876-886.
This study used a prospective adoption design to investigate effects of prenatal and postnatal parent depressive symptom exposure on child hypothalamic-pituitary-adrenal (HPA) activity and associated internalizing symptoms. Birth mother prenatal symptoms and adoptive mother/father postnatal (9-month, 27-month) symptoms were assessed with the Beck Depression Inventory in a sample of 192 families as part of the Early Growth and Development adoption Study. Child morning/evening cortisol levels and child symptoms of internalizing disorders (according to mother/father report on the Child Behavior Checklist) were assessed at 54 months, and birth mother diurnal cortisol was measured at 48 months postnatal. Hierarchical linear modeling was used to test main effects and interactions of parents' symptoms predicting child cortisol, controlling for birth mother cortisol. Prenatal exposure to birth mother symptoms predicted lower child cortisol (main effect), as did postnatal exposure to adoptive parent symptoms (interaction effects). Adoptive mother 9-month symptoms exacerbated cortisol-lowering effects of both concurrent paternal symptoms and later (27-month) maternal symptoms, and the effect of birth mother cortisol. Lower child cortisol, in turn, was associated with higher child internalizing symptoms. Implications are discussed with respect to the intergenerational transmission of depression risk.

Influences of Biological and Adoptive Mothers' Depression and Antisocial Behavior on Adoptees' Early Behavior Trajectories. Kerr DC, Leve LD, Harold GT, Natsuaki MN, Neiderhiser JM, Shaw DS, Reiss D. J Abnorm Child Psychol. 2013 Jul; 41(5): 723-734.
Research clearly demonstrates that parents pass risk for depression and antisocial behavior on to their children. However, most research confounds genetic and environmental mechanisms by studying genetically related individuals. Furthermore, most studies focus on either depression or antisocial behavior in parents or children, despite evidence of co-occurrence and shared etiology, and few consider the early origins of these problems in childhood. The authors estimated the influence of biological and adoptive mothers' depression and antisocial behavior on growth in child externalizing and internalizing behaviors across early childhood using data from a prospective adoption study. Participants were 346 matched triads of

physically healthy children (196 boys; 150 girls), biological mothers (BM), and adoptive mothers (AM). Latent growth curve models were estimated using AM reports of child internalizing and externalizing behaviors at ages 18, 27, and 54 months. Predictors of intercept (18 months) but not slope were identified. BM lifetime histories of major depressive disorder predicted child externalizing behaviors and BM antisocial behavior predicted child internalizing behavior. AM depressive symptoms and antisocial behavior were associated with both child outcomes. AM paths, but not BM paths were partially replicated using adopted fathers' reports of child outcomes. BM obstetric complications, prenatal depressive symptoms, and postnatal adoptive family contact with BM did not account for BM paths. This adoption study distinguished risks conferred by biological mothers' depression and antisocial behavior to children's behaviors from those associated with adoptive mothers' related symptoms. Future studies should examine gene-environment interplay to explain the emergence of serious problem trajectories in later childhood.

Conduct Disorder and Initiation of Substance Use: A Prospective Longitudinal Study. Hopfer C, Salomonsen-Sautel S, Mikulich-Gilbertson S, Min SJ, McQueen M, Crowley T, Young S, Corley R, Sakai J, Thurstone C, Hoffenberg A, Hartman C, Hewitt J. J Am Acad Child Adolesc Psychiatry. 2013 May; 52(5): 511-518.

The objective of this study was to examine the influence of conduct disorder (CD) on substance use initiation. Community adolescents without CD (n = 1,165, mean baseline age = 14.6 years), with CD (n = 194, mean baseline age = 15.3 years), and youth with CD recruited from treatment (n = 268, mean baseline age = 15.7 years) were prospectively followed and re-interviewed during young adulthood (mean ages at follow-up respectively: 20, 20.8, and 24). Young adult retrospective reports of age of substance initiation for 10 substance classes were analyzed using Cox regression analyses. Hazard ratios of initiation for the CD cohorts (community without CD as the reference) at ages 15, 18, and 21 were calculated, adjusting for baseline age, gender, and race/ethnicity. Among community subjects, CD was associated with elevated adjusted hazards for initiation of all substances, with comparatively greater hazard ratios of initiating illicit substances at age 15 years. By age 18, the adjusted hazard ratios remained significant except for alcohol. At age 21, the adjusted hazard ratios were significant only for cocaine, amphetamines, inhalants, and club drugs. A substantial portion of community subjects without CD never initiated illicit substance use. Clinical youth with CD demonstrated similar patterns, with comparatively larger adjusted hazard ratios. CD confers increased risk for substance use initiation across all substance classes at age 15 years, with greater relative risk for illicit substances compared to licit substances. This effect continues until age 18 years, with the weakest effect for alcohol. It further diminishes for other substances by age 21, However, the likelihood of initiating cocaine, amphetamines, inhalants and club drug use among those who have not initiated yet continues to be highly elevated by age 21.

The Nature of Nurture: Disentangling Passive Genotype-Environment Correlation from Family Relationship Influences on Children's Externalizing Problems. Harold GT, Leve LD, Elam KK, Thapar A, Neiderhiser JM, Natsuaki MN, Shaw DS, Reiss D. J Fam Psychol. 2013 Feb; 27(1): 12-21.

The relationship between interparental conflict, hostile parenting, and children's externalizing problems is well established. Few studies, however, have examined the pattern of association underlying this constellation of family and child level variables while controlling for the

possible confounding presence of passive genotype-environment correlation. Using the attributes of 2 genetically sensitive research designs, the present study examined associations among interparental conflict, parent-to-child hostility, and children's externalizing problems among genetically related and genetically unrelated mother-child and father-child groupings. Analyses were conducted separately by parent gender, thereby allowing examination of the relative role of the mother-child and father-child relationships on children's behavioral outcomes. Path analyses revealed that for both genetically related and genetically unrelated parents and children, indirect associations were apparent from interparental conflict to child externalizing problems through mother-to-child and father-to-child hostility. Associations between interparental conflict and parent-to-child hostility across genetically related and genetically unrelated parent-child groupings were significantly stronger for fathers compared to mothers. Results are discussed with respect to the role of passive genotype-environment correlation as a possible confounding influence in interpreting research findings from previous studies conducted in this area. Implications for intervention programs focusing on family process influences on child externalizing problems are also considered.

Selective Impact of Early Parental Responsivity on Adolescent Stress Reactivity. Hackman DA, Betancourt LM, Brodsky NL, Kobrin L, Hurt H, Farah MJ. PLoS One. 2013; 8(3): e58250.

Research in animals has shown that early life experience, particularly parenting behaviors, influences later-life stress reactivity. Despite the tremendous relevance of this finding to human development and brain function, it has not been tested prospectively in humans. In this study two aspects of parenting were measured at age 4 in a sample of healthy, low socioeconomic status, African American children, and stress reactivity was measured in the same children 11-14 years later using a modified version of the Trier Social Stress Test (n = 55). Salivary cortisol was measured before, during and after the stressor and data were analyzed using piecewise hierarchical linear modeling. Parental responsivity, independent of the use of physical discipline, was positively related to cortisol reactivity. Effects were independent of subjective appraisals of the stressor and were also independent of other environmental risk factors and current psychosocial functioning. Therefore this study demonstrates in a novel and precise fashion that early childhood parental responsivity prospectively and independently predicts stress reactivity in adolescence.

Decreased Frontal N-Acetylaspartate Levels in Adolescents Concurrently using both Methamphetamine and Marijuana. Sung YH, Carey PD, Stein DJ, Ferrett HL, Spottiswoode BS, Renshaw PF, Yurgelun-Todd DA. Behav Brain Res. 2013 Jun 1; 246: 154-161.

The potential neurochemical toxicity associated with methamphetamine (MA) or marijuana (MJ) use on the developing adolescent brain is unclear, particularly with regard to individuals with concomitant use of MA and MJ (MA+MJ). In this study, proton magnetic resonance spectroscopy (MRS) was utilized to measure in vivo brain N-acetylaspartate plus N-acetylaspartyl glutamate (tNAA, an indicator of intact neuronal integrity) levels. Three adolescent groups from Cape Town, South Africa completed MRS scans as well as clinical measures including a drug use history. Subjects included (1) nine MA (age=15.7±1.37), (2) eight MA+MJ (age=16.2±1.16) using adolescents and (3) ten healthy controls (age=16.8±0.62). Single voxel spectra were acquired from midfrontal gray matter using a

point-resolved spectroscopy sequence (PRESS). The MRS data were post-processed in the fully automated approach for quantitation of metabolite ratios to phosphocreatine plus creatine (PCr+Cr). A significant reduction in frontal tNAA/PCr+Cr ratios was seen in the MA+MJ group compared to the healthy controls ($p=0.01$, by 7.2%) and to the MA group ($p=0.04$, by 6.9%). Significant relationships were also observed between decreased tNAA/PCr+Cr ratios and drug use history of MA or MJ (total cumulative lifetime dose, age of onset, and duration of MA and MJ exposure) only in the MA+MJ group (all $p<0.05$). These findings suggest that in adolescents, concomitant heavy MA+MJ use may contribute to altered brain metabolites in frontal gray matter. The significant associations between the abnormal tNAA/PCr+Cr ratios and the drug use history suggest that MA+MJ abuse may induce neurotoxicity in a dose-responsive manner in adolescent brain.

Single-Image Vignetting Correction from Gradient Distribution Symmetries. Zheng Y, Lin S, Kang SB, Xiao R, Gee JC, Kambhamettu C. IEEE Trans Pattern Anal Mach Intell. 2013 Jun; 35(6): 1480-1494.
The authors present novel techniques for single-image vignetting correction based on symmetries of two forms of image gradients: semicircular tangential gradients (SCTG) and radial gradients (RG). For a given image pixel, an SCTG is an image gradient along the tangential direction of a circle centered at the presumed optical center and passing through the pixel. An RG is an image gradient along the radial direction with respect to the optical center. The authors observe that the symmetry properties of SCTG and RG distributions are closely related to the vignetting in the image. Based on these symmetry properties, they develop an automatic optical center estimation algorithm by minimizing the asymmetry of SCTG distributions, and also present two methods for vignetting estimation based on minimizing the asymmetry of RG distributions. In comparison to prior approaches to single-image vignetting correction, these methods do not rely on image segmentation and they produce more accurate results. Experiments show these techniques to work well for a wide range of images while achieving a speed-up of 3-5 times compared to a state-of-the-art method.

Influence of Analysis Technique on Measurement of Diffusion Tensor Imaging Parameters. Urger E, Debellis MD, Hooper SR, Woolley DP, Chen S, Provenzale JM. Am J Roentgenol. 2013 May; 200(5): W510-7.
The authors compared results from various methods of analysis of diffusion tensor imaging (DTI) data from a single dataset consisting of 10 healthy adolescents. All subjects were imaged on a single 3-T MRI system (single-shot echo-planar imaging pulse sequence; b value, 1000 s/mm(2)). The authors measured fractional anisotropy (FA), apparent diffusion coefficient (ADC), and axial and radial diffusivity values using 64-pixel rectangular regions of interest (ROIs) in the right side, midline, and left side of the central portion of the splenium of the corpus callosum for fixed (i.e., at same sites in all subjects) and targeted (i.e., at sites of highest FA values) locations. The authors compared results with those obtained using 64-pixel oval ROIs and 100-pixel rectangular ROIs in the same locations. Finally, they compared results from ROI-based methods and from tractography. All comparisons used the Wilcoxon signed rank test and the intraclass correlation of individual values. Compared to tractography, the average of mean ROI-based values was significantly higher for fixed (approximately 14%) and targeted (approximately 39%) FA values and was significantly lower for ADC (approximately 16%) and radial diffusivity (approximately 38%) values. For solely ROI-based

comparisons, statistically significant differences were found in the following comparisons: 64- versus 100-pixel ROI, oval versus rectangular ROI, targeted FA left of midline versus mean targeted FA value, and targeted ROI right of midline versus mean targeted FA value. Markedly different values were obtained when using either ROI- or tractography-based techniques or ROI analysis techniques that differ only relatively slightly.

Prenatal Substance Exposure: Neurobiologic Organization at 1 Month. Conradt E, Sheinkopf SJ, Lester BM, Tronick E, Lagasse LL, Shankaran S, Bada H, Bauer CR, Whitaker TM, Hammond JA; Maternal Lifestyle Study. J Pediatr. 2013 Jun 3. [Epub ahead of print]. The aim of this study was to examine the autonomic nervous system and neurobehavioral response to a sustained visual attention challenge in 1-month-old infants with prenatal substance exposure. The authors measured heart rate, respiratory sinus arrhythmia, and neurobehavior during sustained visual orientation tasks included in the Neonatal Intensive Care Unit Network Neurobehavioral Scale in 1129 1-month-old infants with prenatal substance exposure. Four groups were compared: infants with prenatal cocaine and opiate exposure, infants with cocaine exposure, infants with opiate exposure, and infants with exposure to other substances (ie, alcohol, marijuana, and tobacco). The infants with prenatal exposure to both cocaine and opiates had the highest heart rates and lowest levels of respiratory sinus arrhythmia during a sustained visual attention challenge compared with the other 3 groups. Infants with prenatal cocaine and opiate exposure had poorer quality of movement and more hypertonicity during the Neonatal Intensive Care Unit Network Neurobehavioral Scale examination. They also had more nonoptimal reflexes and stress/abstinence signs compared with infants with prenatal exposure to cocaine only and those with prenatal exposure to alcohol, tobacco, and marijuana. Problems with arousal regulation were identified in infants with prenatal substance exposure. Autonomic dysregulation has been implicated as a mechanism by which these difficulties occur. These results suggest that infants with prenatal exposure to both cocaine and opiates have the greatest autonomic response to the challenge of a sustained visual attention task, possibly putting these infants at risk for problems associated with physiologic and behavioral regulation, a necessary prerequisite for early learning.

CLINICAL NEUROSCIENCE RESEARCH

Repetitive Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex Reduces Nicotine Cue Craving. Li X, Hartwell KT, Owens M, LeMatty T, Borckardt JJ, Hanlon CA, Brady KT, George MS. Biol Psychiat. 2013; 73(8): 714–720.
Repetitive transcranial magnetic stimulation (rTMS) can noninvasively stimulate the brain and transiently amplify or block behaviors mediated through a region. The authors hypothesized that a single high-frequency rTMS session over the left dorsolateral prefrontal cortex (DLPFC) would reduce cue craving for cigarettes compared with a sham TMS session. Sixteen non-treatment-seeking, nicotine-dependent participants were randomized to receive either real high-frequency rTMS (10 Hz, 100% resting motor threshold, 5-sec on, 10-sec off for 15 min; 3000 pulses) or active sham (eSham) TMS over the DLPFC in two visits with 1 week between visits. The participants received cue exposure before and after rTMS and rated their craving after each block of cue presentation. Stimulation of the left DLFPC with real, but not sham, rTMS reduced craving significantly from baseline (64.1±5.9 vs. 45.7±6.4, $t = 2.69$, $p = .018$). When compared with neutral cue craving, the effect of real TMS on cue craving was significantly greater than the effect of sham TMS (12.5±10.4 vs. –9.1±10.4; $t = 2.07$, $p = .049$). More decreases in subjective craving induced by TMS correlated positively with higher Fagerström Test for Nicotine Dependence score ($r = .58$, $p = .031$) and more cigarettes smoked per day ($r = .57$, $p = .035$). One session of high-frequency rTMS (10 Hz) of the left DLPFC significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants. Additional studies are needed to explore rTMS as an aid to smoking cessation.

Reduction of Cue-induced Craving Through Realtime Neurofeedback in Nicotine Users: The Role of Region of Interest Selection and Multiple Visits. Hanlon CA, Hartwell KJ, Canterberry M, Li X, Owens M, Lematty T, Prisciandaro JJ, Borckardt J, Brady KT, George MS. Psychiat Res 2013; 213(1): 79-81. [doi: 10.1016/j.pscychresns.2013.03.003. 2013 May 15. [Epub ahead of print].
This multi-visit, real-time functional magnetic resonance imaging feedback study demonstrates that treatment-seeking smokers can effectively modulate their behavioral and brain responses to smoking cues. They are more effective at decreasing activity in functionally defined regions involved in "craving" (e.g. ventral anterior cingulate cortex (vACC)) rather than increasing activity in regions involved in "resisting" (e.g. dorsal medial prefrontal cortex (dmPFC)).

Functional Brain Networks Associated with Cognitive Control, Cocaine Dependence, and Treatment Outcome. Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearlson GD, Potenza MN. Psychol Addict Behav 2012 Jul 9. [Epub ahead of print].
Individuals with cocaine dependence often evidence poor cognitive control. The purpose of this exploratory study was to investigate networks of functional connectivity underlying cognitive control in cocaine dependence and examine the relationship of the networks to the disorder and its treatment. Independent component analysis (ICA) was applied to fMRI data to investigate if regional activations underlying cognitive control processes operate in functional networks, and whether these networks relate to performance and treatment outcome measures in cocaine dependence. Twenty patients completed a Stroop task during fMRI prior to entering outpatient treatment and were compared to 20 control participants. ICA identified five distinct functional networks related to cognitive control interference events. Cocaine-dependent

patients displayed differences in performance-related recruitment of three networks. Reduced involvement of a "top-down" fronto-cingular network contributing to conflict monitoring correlated with better treatment retention. Greater engagement of two "bottom-up" subcortical and ventral prefrontal networks related to cue-elicited motivational processing correlated with abstinence during treatment. The identification of subcortical networks linked to cocaine abstinence and cortical networks to treatment retention suggests that specific circuits may represent important, complementary targets in treatment development for cocaine dependence.

The Impact of Sex on Brain Responses to Smoking Cues: a Perfusion fMRI Study. Wetherill RR, Young KA, Jagannathan K, Shin J, O'Brien CP, Childress AR, Franklin TR. Biol Sex Diff. 2013 April. [Epub ahead of print. doi:10.1186/2042-6410-4-9].
Anecdotal and clinical theories purport that females are more responsive to smoking cues, yet few objective, neurophysiological examinations of these theories have been conducted. The current study examines the impact of sex on brain responses to smoking cues. Fifty-one (31 males) cigarette-dependent sated smokers underwent pseudo-continuous arterial spin-labeled perfusion functional magnetic resonance imaging during exposure to visual smoking cues and non-smoking cues. Brain responses to smoking cues relative to non-smoking cues were examined within males and females separately and then compared between males and females. Cigarettes-smoked-per-day was included in analyses as a covariate. Both males and females showed increased responses to smoking cues compared to non-smoking cues with males exhibiting increased medial orbitofrontal cortex and ventral striatum/ventral pallidum responses, and females showing increased medial orbitofrontal cortex responses. Direct comparisons between male and female brain responses revealed that males showed greater bilateral hippocampal/amygdala activation to smoking cues relative to non-smoking cues. Males and females exhibit similar responses to smoking cues relative to non-smoking cues in a priori reward-related regions; however, direct comparisons between sexes indicate that smoking cues evoke greater bilateral hippocampal/amygdalar activation among males. Given the current literature on sex differences in smoking cue neural activity is sparse and incomplete, these results contribute to our knowledge of the neurobiological underpinnings of drug cue reactivity.

Content Matters: Neuroimaging Investigation of Brain and Behavioral Impact of Televised Anti-Tobacco Public Service Announcements. Wang AL, Ruparel K, Loughead JW, Strasser AA, Blady SJ, Lynch KG, Romer D, Cappella JN, Lerman C, Langleben DD. J Neurosci 2013; 33(17): 7420-7427.
Televised public service announcements are video ads that are a key component of public health campaigns against smoking. Understanding the neurophysiological correlates of anti-tobacco ads is an important step toward novel objective methods of their evaluation and design. In the present study, the authors used functional magnetic resonance imaging (fMRI) to investigate the brain and behavioral effects of the interaction between content ("argument strength," AS) and format ("message sensation value," MSV) of anti-smoking ads in humans. Seventy-one nontreatment-seeking smokers viewed a sequence of 16 high or 16 low AS ads during an fMRI scan. Dependent variables were brain fMRI signal, the immediate recall of the ads, the immediate change in intentions to quit smoking, and the urine levels of a major nicotine metabolite cotinine at a 1 month follow-up. Whole-brain ANOVA revealed that AS and MSV interacted in the inferior frontal, inferior parietal, and fusiform gyri; the precuneus;

and the dorsomedial prefrontal cortex (dMPFC). Regression analysis showed that the activation in the dMPFC predicted the urine cotinine levels 1 month later. These results characterize the key brain regions engaged in the processing of persuasive communications and suggest that brain fMRI response to anti-smoking ads could predict subsequent smoking severity in nontreatment-seeking smokers. These findings demonstrate the importance of the quality of content for objective ad outcomes and suggest that fMRI investigation may aid the prerelease evaluation of televised public health ads.

Treatment for Tobacco Dependence: Effect on Brain Nicotinic Acetylcholine Receptor Density. Brody AL, Mukhin AG, Stephanie Shulenberger, Mamoun MS, Kozman M, Phuong J, Neary M, Luu T, Mandelkern MA. Neuropsychopharm 2013; 38(8): 1548-1556. Cigarette smoking leads to up-regulation of brain nicotinic acetylcholine receptors (nAChRs), including the common α4β2* nAChR subtype. Although a substantial percentage of smokers receive treatment for tobacco dependence with counseling and/or medication, the effect of a standard course of these treatments on nAChR up-regulation has not yet been reported. In the present study, 48 otherwise healthy smokers underwent positron emission tomography (PET) scanning with the radiotracer 2-FA (for labeling α4β2* nAChRs) before and after treatment with either cognitive-behavioral therapy, bupropion HCl, or pill placebo. Specific binding volume of distribution (VS/fP), a measure proportional to α4β2* nAChR density, was determined for regions known to have nAChR up-regulation with smoking (prefrontal cortex, brainstem, and cerebellum). In the overall study sample, significant decreases in VS/fP were found for the prefrontal cortex, brainstem, and cerebellum of -20 (±35), -25 (±36), and -25 (±31)%, respectively, which represented movement of VS/fP values toward values found in non-smokers (mean 58.2% normalization of receptor levels). Participants who quit smoking had significantly greater reductions in VS/fP across regions than non-quitters, and correlations were found between reductions in cigarettes per day and decreases in VS/fP for brainstem and cerebellum, but there was no between-group effect of treatment type. Thus, smoking reduction and cessation with commonly used treatments (and pill placebo) lead to decreased α4β2* nAChR densities across brain regions. Study findings could prove useful in the treatment of smokers by providing encouragement with the knowledge that decreased smoking leads to normalization of specific brain receptors.

Concurrent Use of Khat and Tobacco is Associated with Verbal Learning and Delayed Recall Deficits. Hoffman R, Al'absi M. Addiction. 2013 May 28. [Epub ahead of print]. The present study assessed whether cigarette smokers who are also regular khat users would demonstrate greater impairments in verbal learning and recall compared to both non-smokers who are khat users and control subjects. An independent measures, between-subjects design with two co-variates. An outpatient, university research center in Taiz, Yemen. Subjects were 175 Yemeni college students (90 men, 85 women) ranging in age from 18 to 38. Seventy-Five subjects were self-reported chronic cigarette smokers and khat users, 48 non-smoking subjects were self-reported to be chronic khat users and 52 non-smoking subjects reported no current use or history of khat use. Verbal learning and verbal memory recall was assessed by subject performance on the Arabic version of Rey Auditory Verbal Learning Test (RAVLT). There were statistically significant differences ($p<0.05$) observed in RAVLT acquisition learning Trials 2-5 and on delayed recall measures between concurrent khat and cigarette users compared to both the khat only group and the control group of nonusers of khat and cigarettes.

On each of these trials, concurrent users recalled fewer words, demonstrating a slowed rate of verbal learning. This same pattern of performance was also seen on delayed recall measures. Khat use alone did not affect immediate or delayed recall of previously learned words. Khat users who smoke cigarettes have lower rate of verbal learning and delayed recall of previously learned verbal material than Khat users who do not smoke cigarettes. This may be due to pre-existing differences between these groups of subjects.

Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana in Daily Marijuana Smokers. Cooper ZD, Comer SD, Haney M. Neuropsychopharm 2013 Apr 22. [Epub ahead of print].

Recent studies have demonstrated the therapeutic potential of cannabinoids to treat pain, yet none have compared the analgesic effectiveness of smoked marijuana to orally administered Δ9-tetrahydrocannabinol (THC; dronabinol). This randomized, placebo-controlled, double-dummy, double-blind study compared the magnitude and duration of analgesic effects of smoked marijuana and dronabinol under well-controlled conditions using a validated experimental model of pain. Healthy male (N=15) and female (N=15) daily marijuana smokers participated in this outpatient study comparing the analgesic, subjective, and physiological effects of marijuana (0.00, 1.98, or 3.56% THC) to dronabinol (0, 10, or 20 mg). Pain response was assessed using the cold-pressor test (CPT): participants immersed their left hand in cold water (4°C), and the time to report pain (pain sensitivity) and withdraw the hand from the water (pain tolerance) were recorded. Subjective pain and drug effect ratings were also measured as well as cardiovascular effects. Compared with placebo, marijuana and dronabinol decreased pain sensitivity (3.56%; 20 mg), increased pain tolerance (1.98%; 20 mg), and decreased subjective ratings of pain intensity (1.98, 3.56%; 20 mg). The magnitude of peak change in pain sensitivity and tolerance did not differ between marijuana and dronabinol, although dronabinol produced analgesia that was of a longer duration. Marijuana (1.98, 3.56%) and dronabinol (20 mg) also increased abuse-related subjective ratings relative to placebo; these ratings were greater with marijuana. These data indicate that under controlled conditions, marijuana and dronabinol decreased pain, with dronabinol producing longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana.

Conditioned Preference to a Methamphetamine-Associated Contextual Cue in Humans. Mayo LM, Fraser D, Childs E, Momenan R, Hommer DW, de Wit H, Heilig M. Neuropsycho-pharm 2013; 38(6): 921-929.

Classical conditioning is widely used to study motivational properties of addictive drugs in animals, but has rarely been used in humans. The authors established a procedure suitable for studying the neurobiology and individual determinants of classical conditioning in humans. Healthy volunteers were randomly assigned to four groups that received methamphetamine or placebo in the presence of distinctive environmental cues under paired or unpaired conditions. During each session, subjects performed tasks known to activate the ventral striatum. Tasks were performed in the presence of a distinctive context, consisting of a screen background image of a beach or mountains, accompanied by corresponding sounds. Separate groups of subjects carried out the tasks under high ($35-50) or low ($5-20) reward conditions. Within each of the two reward conditions, one group (paired) received methamphetamine (20 mg, oral) or placebo consistently associated with one of the contexts, while the other (unpaired)

received drug or placebo unrelated to context. A fifth group (paired) performed the tasks with contextual cues but in the absence of monetary incentives. Before and after conditioning, participants carried out a series of forced choice tasks for the contextual cues, and change of preference over time was analyzed. All paired groups showed a significant increase in preference for the drug-associated context, with a linear trend for increase across the levels of reward. Preference was unrelated to subjective drug effects, and did not change in the unpaired group. These data support the translational utility of our conditioning procedure for studies of reward mechanisms in humans.

Methamphetamine-Induced Increases in Putamen Gray Matter Associated with Inhibitory Control. Groman SM, Morales AM, Lee B, London ED, Jentsch JD. Psychopharm (Berl) 2013 Jun 10. [Epub ahead of print].
Problematic drug use is associated with difficulty in exerting self-control over behaviors, and this difficulty may be a consequence of atypical morphometric characteristics that are exhibited by drug-experienced individuals. The extent to which these structural abnormalities result from drug use or reflect neurobiological risk factors that predate drug use, however, is unknown. The purpose of this study is to determine how methamphetamine affects corticostriatal structure and how drug-induced changes relate to alterations in inhibitory control. Structural magnetic resonance images and positron emission tomography (PET) scans, assessing dopamine D2-like receptor and transporter availability, were acquired in monkeys trained to acquire, retain, and reverse three-choice visual discrimination problems before and after exposure to an escalating dose regimen of methamphet-amine (or saline, as a control). Voxel-based morphometry was used to compare changes in corticostriatal gray matter between methamphetamine- and saline-exposed monkeys. The change in gray matter before and after the dosing regimen was compared to the change in the behavioral performance and in dopaminergic markers measured with PET. Methamphetamine exposure, compared to saline, increased gray matter within the right putamen. These changes were positively correlated with changes in performance of methamphetamine-exposed monkeys in the reversal phase, and were negatively correlated with alterations in D2-like receptor and DAT availability. The results provide the first evidence that exposure to a methamphetamine dosing regimen that resembles human use alters the structural integrity of the striatum and that gray-matter abnormalities detected in human methamphetamine users are due, at least in part, to the pharmacological effects of drug experience.

Resisting the Urge to Smoke and Craving During a Smoking Quit Attempt on Varenicline: Results From a Pilot fMRI Study. Hartwell KJ, Lematty T, McRae-Clark AL, Gray KM, George MS, Brady KT. Am J Drug Alcohol Abuse 2013; 39(2): 92-98.
Varenicline has been shown to reduce cigarette craving during a quit attempt. The authors used BOLD fMRI to explore differences in smoking cue reactivity at baseline and after five weeks of varenicline smoking cessation treatment. Treatment-seeking nicotine-dependent adult smokers underwent BOLD fMRI scans with block presentation of visual smoking, neutral, and rest cues under two conditions: craving or resisting the urge to smoke at baseline and following 5 weeks of standard varenicline therapy. Data were analyzed using FMRI Expert Analysis Tool, version 5.98 of Functional Magnetic Imaging of the Brain Software Library focused on the smoking vs. neutral cue contrast at the individual and group level, $Z>2.3$ with cluster threshold $p=0.05$. Twenty-one participants were scanned at baseline and 16

completed the study; 10 were abstinent at the 2(nd) session, confirmed with urinary cotinine. In the Crave Condition no significant differences were found between the abstinent and non-abstinent groups at either time point. During the baseline Resist Condition, the abstinent group compared to the non-abstinent group demonstrated activation in a distributed network involved in alertness, learning and memory. Additionally, within the abstinent group, increased activation of the superior frontal gyrus was found at baseline compared to week 5. Successful smoking cessation with varenicline is associated with increased activation, prior to a quit attempt, in brain areas related to attentiveness and memory while resisting the urge to smoke. Varenicline may exert effects by both reducing craving and enhancing resistance to smoking urges during cue-elicited craving.

Rational Temporal Predictions Can Underlie Apparent Failures to Delay Gratification. McGuire JT, Kable JW. Psychol Rev 2013; 120(2): 395-410. 2013 Mar 4. [doi: 10.1037/a0031910. Epub ahead of print].

An important category of seemingly maladaptive decisions involves failure to postpone gratification. A person pursuing a desirable long-run outcome may abandon it in favor of a short-run alternative that has been available all along. Here the authors present a theoretical framework in which this seemingly irrational behavior emerges from stable preferences and veridical judgments. This account recognizes that decision makers generally face uncertainty regarding the time at which future outcomes will materialize. When timing is uncertain, the value of persistence depends crucially on the nature of a decision maker's prior temporal beliefs. Certain forms of temporal beliefs imply that a delay's predicted remaining length increases as a function of time already waited. In this type of situation, the rational, utility-maximizing strategy is to persist for a limited amount of time and then give up. The authors show empirically that people's explicit predictions of remaining delay lengths indeed increase as a function of elapsed time in several relevant domains, implying that temporal judgments offer a rational basis for limiting persistence. The authors then develop their framework into a simple working model and show how it accounts for individual differences in a laboratory task (the well-known "marshmallow test"). They conclude that delay-of-gratification failure, generally viewed as a manifestation of limited self-control capacity, can instead arise as an adaptive response to the perceived statistics of one's environment.

Greater Risk Sensitivity of Dorsolateral Prefrontal Cortex in Young Smokers than in Nonsmokers. , Schonberg T, Mumford J, Kohno M, Poldrack RA, London ED. Psychopharm (Berl). 2013 May 5. [Epub ahead of print].

Despite a national reduction in the prevalence of cigarette smoking, ~19 % of the adult US population persists in this behavior, with the highest prevalence among 18-25-year-olds. Given that the choice to smoke imposes a known health risk, clarification of brain function related to decision-making, particularly involving risk-taking, in smokers may inform prevention and smoking cessation strategies. This study aimed to compare brain function related to decision-making in young smokers and nonsmokers The Balloon Analogue Risk Task (BART) is a computerized risky decision-making task in which participants pump virtual balloons, each pump associated with an incremental increase in potential payoff on a given trial but also with greater risk of balloon explosion and loss of payoff. The authors used this task to compare brain activation associated with risky decision-making in smokers (n=18) and nonsmokers (n=25), while they performed the BART during functional magnetic resonance imaging

(fMRI). The participants were young men and women, 17-21 years of age. Risk level (number of pumps) modulated brain activation in the right dorsolateral and ventrolateral prefrontal cortices more in smokers than in nonsmokers, and smoking severity (Heaviness of Smoking Index) was positively related to this modulation in an adjacent frontal region. Given evidence for involvement of the right dorsolateral and ventrolateral prefrontal cortices in inhibitory control, these findings suggest that young smokers have a different contribution of prefrontal cortical substrates to risky decision-making than nonsmokers. Future studies are warranted to determine whether the observed neurobiological differences precede or result from smoking.

Error Processing and Gender-Shared and -Specific Neural Predictors of Relapse in Cocaine Dependence. Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CS. Brain 2013; 136(Pt 4): 1231-1244.
Deficits in cognitive control are implicated in cocaine dependence. Previously, combining functional magnetic resonance imaging and a stop signal task, the authors demonstrated altered cognitive control in cocaine-dependent individuals. However, the clinical implications of these cross-sectional findings and, in particular, whether the changes were associated with relapse to drug use, were not clear. In a prospective study, the authors recruited 97 treatment-seeking individuals with cocaine dependence to perform the stop signal task during functional magnetic resonance imaging and participate in follow-up assessments for 3 months, during which time cocaine use was evaluated with timeline follow back and ascertained by urine toxicology tests. Functional magnetic resonance imaging data were analysed using general linear models as implemented in Statistical Parametric Mapping 8, with the contrast 'stop error greater than stop success trials' to index error processing. Using voxel-wise analysis with logistic and Cox regressions, the authors identified brain activations of error processing that predict relapse and time to relapse. In females, decreased error-related activations of the thalamus and dorsal anterior cingulate cortex predicted relapse and an earlier time to relapse. In males, decreased error-related activations of the dorsal anterior cingulate cortex and left insula predicted relapse and an earlier time to relapse. These regional activations were validated with data resampling and predicted relapse with an average area under the curve of 0.849 in receiver operating characteristic analyses. These findings provide direct evidence linking deficits in cognitive control to clinical outcome in a moderate-sized cohort of cocaine-dependent individuals. These results may provide a useful basis for future studies to examine how psychosocial factors interact with cognitive control to determine drug use and to evaluate the efficacy of pharmacological or behavioural treatment in remediating deficits of cognitive control in cocaine addicts.

Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. J Pain 2013; 14(2): 136-148.
The authors conducted a double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Thirty-nine patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling medium-dose (3.53%), low-dose (1.29%), or placebo cannabis with the primary outcome being visual analog scale pain intensity. Psychoactive side effects and neuropsychological performance were also evaluated. Mixed-effects regression models demonstrated an analgesic response to vaporized cannabis. There was no significant difference between the 2 active dose groups' results ($P > .7$). The

number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium-versus low-dose. As these NNTs are comparable to those of traditional neuropathic pain medications, cannabis has analgesic efficacy with the low dose being as effective a pain reliever as the medium dose. Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours. Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain. The analgesia obtained from a low dose of delta-9-tetrahydrocannabinol (1.29%) in patients, most of whom were experiencing neuropathic pain despite conventional treatments, is a clinically significant outcome. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning.

Alcohol-Dependent Individuals Discount Sex at Higher Rates than Controls. Jarmolowicz DP, Bickel WK, Gatchalian KM. Drug Alcohol Depend 2013; 131(3): 320-323.
Research on delay discounting has expanded our understanding of substance dependence in many ways. Recently, orderly discounting of sexual rewards has been demonstrated in both substance-dependent individuals, and healthy controls. Less clear, however, is if rates of sexual discounting are higher than controls in alcohol-dependent-individuals. 20 alcohol-dependent individuals and 21 healthy control participants completed two delay-discounting tasks. One task involved monetary rewards, whereas the other involved the discounting of sexual rewards (i.e., number of sex acts). Alcohol dependent individuals discounted sexual rewards at significantly higher rates than did controls. There was a trend toward, but not a similarly significant relation for the discounting of monetary rewards. Rates of sexual discounting are elevated in alcohol dependent individuals. If this relation is replicated in other at risk populations, the rapid devaluation of sexual rewards may be a laboratory marker of impulsive sexual choices.

Pain and Associated Substance Use among Opioid Dependent Individuals Seeking Office-based Treatment with Buprenorphine-Naloxone: a Needs Assessment Study. Barry DT, Savant JD, Beitel M, Cutter CJ, Moore BA, Schottenfeld RS, Fiellin DA. Am J Addict 2013; 22(3): 212-217.
A paucity of studies has examined the pain experiences of opioid dependent individuals seeking office-based buprenorphine-naloxone treatment (BNT). The authors set out to examine, among those seeking BNT: (a) the prevalence of pain types (i.e., recent pain, chronic pain), (b) the characteristics of pain (intensity, frequency, duration, interference, location, and genesis), and (c) substance use to alleviate pain. They surveyed 244 consecutive individuals seeking office-based BNT for opioid dependence about physical pain and associated substance use. Thirty-six percent of respondents reported chronic pain (CP) (i.e., pain lasting at least 3 months) and 36% reported "some pain" (SP) (i.e., past week pain not meeting the threshold for CP). In comparison to SP respondents, those with CP were, on average, older; reported greater current pain intensity, pain frequency, typical pain duration, typical pain intensity, and typical pain interference; were more likely to report shoulder or pelvis and less likely to report stomach or arms as their most bothersome pain location; and were more likely to report accident or nerve damage and less likely to report opioid withdrawal as the genesis of their pain. Both pain subgroups reported similarly high rates of past-week substance use to alleviate

pain. The high rates of pain and self-reported substance use to manage pain suggest the importance of assessing and addressing pain in BNT patients.

Anger Regulation Style, Anger Arousal and Acute Pain Sensitivity: Evidence for an Endogenous Opioid "Triggering" Model. Burns JW, Bruehl S, Chont M. J Behav Med. 2013 Apr 28. [Epub ahead of print].
Findings suggest that greater tendency to express anger is associated with greater sensitivity to acute pain via endogenous opioid system dysfunction, but past studies have not addressed the role of anger arousal. The authors used a 2 × 2 factorial design with Drug Condition (placebo or opioid blockade with naltrexone) crossed with Task Order (anger-induction/pain-induction or pain-induction/anger-induction), and with continuous Anger-out Subscale scores. Drug × Task Order × Anger-out Subscale interactions were tested for pain intensity during a 4-min ischemic pain task performed by 146 healthy people. A significant Drug × Task Order × Anger-out Subscale interaction was dissected to reveal different patterns of pain intensity changes during the pain task for high anger-out participants who underwent pain-induction prior to anger-induction compared to those high in anger-out in the opposite order. Namely, when angered prior to pain, high anger-out participants appeared to exhibit low pain intensity under placebo that was not shown by high anger-out participants who received naltrexone. Results hint that people with a pronounced tendency to express anger may suffer from inadequate opioid function under simple pain-induction, but may experience analgesic benefit to some extent from the opioid triggering properties of strong anger arousal.

Resting-State Synchrony in Short-Term versus Long-Term Abstinent Alcoholics. Camchong J, Stenger VA, Fein G. Alcohol Clin Exp Res. 2013 May; 37(5): 794-803.
The authors previously reported that when compared with controls, long-term abstinent alcoholics (LTAA) have increased resting-state synchrony (RSS) of the inhibitory control network and reduced synchrony of the appetitive drive network, and hypothesized that these levels of synchrony are adaptive and support the behavioral changes required to maintain abstinence. In this study, the authors investigate whether these RSS patterns can be identified in short-term abstinent alcoholics (STAA). Resting-state functional magnetic resonance imaging data were collected from 27 STAA, 23 LTAA, and 23 nonsubstance abusing controls (NSAC). The authors examined baseline RSS using seed-based measures. They found ordered RSS effects from NSAC to STAA and then to LTAA within both the appetitive drive and executive control networks: increasing RSS of the executive control network and decreasing RSS of the reward processing network. Finally, they found significant correlations between strength of RSS in these networks and (i) cognitive flexibility, and (ii) current antisocial behavior. Findings are consistent with an adaptive progression of RSS from short- to long-term abstinence, so that, compared with normal controls, the synchrony (i) within the reward network progressively decreases, and (ii) within the executive control network progressively increases.

Substance Use Is a Risk Factor for Neurocognitive Deficits and Neuropsychiatric Distress in Acute and Early HIV Infection. Weber E, Morgan EE, Iudicello JE, Blackstone K, Grant I, Ellis RJ, Letendre SL, Little S, Morris S, Smith DM, Moore DJ, Woods SP; TMARC Group. J Neurovirol 2013; 19(1): 65-74.

The acute and early stages of HIV infection (AEH) are characterized by substantial viral replication, immune activation, and alterations in brain metabolism. However, little is known about the prevalence and predictors of neurocognitive deficits and neuropsychiatric disturbances during this period. The present study examined the impact of demographic, HIV disease, and substance use factors on HIV-associated neurocognitive impairment and self-reported neuropsychiatric distress among 46 antiretroviral-naive adults with median duration of infection of 75 days relative to a sample of 21 HIV seronegative (HIV-) adults with comparable demographics and risk factors. Participants were administered a brief neurocognitive battery that was adjusted for demographics and assessed executive functions, memory, psychomotor speed, and verbal fluency, as well as the Profile of Mood States, a self-report measure of neuropsychiatric distress. Odds ratios revealed that AEH participants were nearly four times more likely than their seronegative counterparts to experience neurocognitive impairment, particularly in the areas of learning and information processing speed. Similarly, AEH was associated with a nearly fivefold increase in the odds of neuropsychiatric distress, most notably in anxiety and depression. Within the AEH sample, HIV-associated neurocognitive impairment was associated with problematic methamphetamine use and higher plasma HIV RNA levels, whereas neuropsychiatric distress was solely associated with high-risk alcohol use. Extending prior neuroimaging findings, the results from this study indicate that HIV-associated neurocognitive impairment and neuropsychiatric distress are highly prevalent during AEH and are associated with high-risk substance use.

Altered Risk-related Processing in Substance Users: Imbalance of Pain and Gain. Gowin JL, Mackey S, Paulus MP. Drug and Alcohol Dependence 2013; [10.1016/j.drugalcdep. 2013.03.019].

Substance use disorders (SUDs) can be conceptualized as a form of risk-taking behavior with the potential for highly aversive outcomes such as health or legal problems. Risky decision-making likely draws upon several related brain processes involved in estimations of value and risk, executive control, and emotional processing. SUDs may result from a dysfunction in one or more of these cognitive processes. The authors performed a systematic literature review of functional neuroimaging studies examining risk-related decision making in individuals with SUDs. A quantitative meta-analysis tool (GingerALE) and qualitative approach was used to summarize the imaging results. Meta-analysis findings indicate that individuals with SUDs exhibit differences in neural activity relative to healthy controls during risk-taking in the anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, striatum, insula, and somatosensory cortex. In addition, a qualitative review of the literature suggests that individuals with SUDs may have altered function in the amygdala and ventromedial prefrontal cortex. The neuroimaging literature reveals that several neural substrates involved in the computation of risk may function suboptimally in SUDs. Future research is warranted to elucidate which computational processes are affected, whether dysfunctional risk-related processing recovers with sobriety, and whether different drugs of abuse have specific effects on risk-taking.

Are There Volumetric Brain Differences Associated with the Use of Cocaine and Amphetamine-type Stimulants? Mackey S, Paulus M. Neuroscience and Biobehavioral Reviews 2013; 37(3):300–316.
While a large number of studies have examined brain volume differences associated with cocaine use, much less is known about structural differences related to amphetamine-type stimulant (ATS) use. What is known about cocaine may help to interpret emerging information on the interaction of brain volume with ATS consumption. To date, volumetric studies on the two types of stimulant have focused almost exclusively on brain differences associated with chronic use. There is considerable variability in the findings between studies which may be explained in part by the wide variety of methodologies employed. Despite this variability, seven recurrent themes are worth noting: (1) loci of lower cortical volume (approximately 10% on average) are consistently reported, (2) almost all studies indicate less volume in all or parts of the frontal cortex, (3) more specifically, a core group of studies implicate the ventromedial prefrontal cortex (including the medial portion of the orbital frontal cortex) and (4) the insula, (5) an enlarged striatal volume has been repeatedly observed, (6) reports on volume differences in the hippocampus and amygdala have been equivocal, (7) evidence supporting differential interaction of brain structure with cocaine vs. ATS is scant but the volume of all or parts of the temporal cortex appear lower in a majority of studies on cocaine but not ATS. Future research should include longitudinal designs on larger sample sizes and examine other stages of exposure to psychostimulants.

Decreased Frontal Lobe Phosphocreatine Levels in Methamphetamine Users. Sung Y-H, Yurgelun-Todd DA, Shi X-F, Kondo DG, Lundberg KJ, McGlade EC, Hellem TL, Huber RS, Fiedler KK, Harrell RE, Nickerson BR, Kim S-E, Jeong E-K, Renshaw PF. Drug and Alcohol Dependence 2013; 129(1-2): 102–109.
Mitochondria-related mechanisms have been suggested to mediate methamphetamine (METH) toxicity. However, changes in brain energetics associated with high-energy phosphate metabolism have not been investigated in METH users. Phosphorus-31 ((31)P) magnetic resonance spectroscopy (MRS) was used to evaluate changes in mitochondrial high energy phosphates, including phosphocreatine (PCr) and β-nucleoside triphosphate (β-NTP, primarily ATP in brain) levels. The authors hypothesized that METH users would have decreased high-energy PCr levels in the frontal gray matter. Study participants consisted of 51 METH (age=32.8±6.7) and 23 healthy comparison (age=31.1±7.5) subjects. High-energy phosphate metabolite levels were compared between the groups and potential gender differences were explored. METH users had lower ratios of PCr to total pool of exchangeable phosphate (PCr/TPP) in the frontal lobe as compared to the healthy subjects (p=.001). The lower PCr levels in METH subjects were significantly associated with lifetime amount of METH use (p=.003). A sub-analysis for gender differences revealed that female METH users, who had lower daily amounts (1.1±1.0g) of METH use than males (1.4±1.7g), had significantly lower PCr/TPP ratios than male METH users, controlling for the amount of METH use (p=.02). The present findings suggest that METH compromises frontal lobe high-energy phosphate metabolism in a dose-responsive manner. These findings also suggest that the abnormality in frontal lobe high-energy phosphate metabolism might be more prominent in female than in male METH users. This is significant as decreased PCr levels have been associated with depressive symptoms, and poor responses to antidepressant treatment have been reported in those with decreased PCr levels.

Pre-encoding Administration of Amphetamine or THC Preferentially Modulates Emotional Memory in Humans. Ballard ME, Gallo DA, de Wit H. Psychopharmacology 2013; 226(3): 515–529.
Many addictive drugs are known to have effects on learning and memory, and these effects could motivate future drug use. Specifically, addictive drugs may affect memory of emotional events and experiences in ways that are attractive to some users. However, few studies have investigated the effects of addictive drugs on emotional memory in humans. This study examined the effects of the memory-enhancing drug dextroamphetamine (AMP) and the memory-impairing drug Δ(9)-tetrahydrocannabinol (THC) on emotional memory in healthy volunteers. Participants completed three experimental sessions across which they received capsules containing placebo and two doses of either AMP (10 and 20 mg; N = 25) or THC (7.5 and 15 mg; N = 25) before viewing pictures of positive (pleasant), neutral, and negative (unpleasant) scenes. Memory for the pictures was assessed 2 days later, under drug-free conditions. Relative to placebo, memory for emotional pictures was improved by AMP and impaired by THC, but neither drug significantly affected memory for unemotional pictures. Positive memory biases were not observed with either drug, and there was no indication that the drugs' memory effects were directly related to their subjective or physiological effects alone. This study provides the first clear evidence that stimulant drugs can preferentially strengthen, and cannabinoids can preferentially impair, memory for emotional events in humans. Although addictive drugs do not appear to positively bias memory, the possibility remains that these drugs' effects on emotional memory could influence drug use among certain individuals.

Self-regulatory Depletion Increases Emotional Reactivity in the Amygdala. Wagner DD, Heatherton TF. Social Cognitive and Affective Neuroscience 2013; 8(4): 410–417.
The ability to self-regulate can become impaired when people are required to engage in successive acts of effortful self-control, even when self-control occurs in different domains. Here, the authors used functional neuroimaging to test whether engaging in effortful inhibition in the cognitive domain would lead to putative dysfunction in the emotional domain. Forty-eight participants viewed images of emotional scenes during functional magnetic resonance imaging in two sessions that were separated by a challenging attention control task that required effortful inhibition (depletion group) or not (control group). Compared to the control group, depleted participants showed increased activity in the left amygdala to negative but not to positive or neutral scenes. Moreover, whereas the control group showed reduced amygdala activity to all scene types (i.e. habituation), the depletion group showed increased amygdala activity relative to their pre-depletion baseline; however this was only significant for negative scenes. Finally, depleted participants showed reduced functional connectivity between the left amygdala and ventromedial prefrontal cortex during negative scene processing. These findings demonstrate that consuming self-regulatory resources leads to an exaggerated neural response to emotional material that appears specific to negatively valenced stimuli and further suggests a failure to recruit top-down prefrontal regions involved in emotion regulation.

EPIDEMIOLOGY RESEARCH

Estimating the Prevalence Of Opioid Diversion By ''Doctor Shoppers'' In the United States. McDonald DC, Carlson KE. PLoS ONE 2013; 8(7): e69241. doi:10.1371/journal.pone.0069241.

Abuse of prescription opioid analgesics is a serious threat to public health, resulting in rising numbers of overdose deaths and admissions to emergency departments and treatment facilities. Absent adequate patient information systems, "doctor shopping" patients can obtain multiple opioid prescriptions for nonmedical use from different unknowing physicians. The present study estimates the prevalence of doctor shopping in the US and the amounts and types of opioids involved. The sample included records for 146.1 million opioid prescriptions dispensed during 2008 by 76% of US retail pharmacies. Prescriptions were linked to unique patients and weighted to estimate all prescriptions and patients in the nation. Finite mixture models were used to estimate different latent patient populations having different patterns of using prescribers. On average, patients in the extreme outlying population (0.7% of purchasers), presumed to be doctor shoppers, obtained 32 opioid prescriptions from 10 different prescribers. They bought 1.9% of all opioid prescriptions, constituting 4% of weighed amounts dispensed. The authors conclude that their data did not provide information to make a clinical diagnosis of individuals. Very few of these patients can be classified with certainty as diverting drugs for nonmedical purposes. However, even patients with legitimate medical need for opioids who use large numbers of prescribers may signal dangerously uncoordinated care. To close the information gap that makes doctor shopping and uncoordinated care possible, states have created prescription drug monitoring programs to collect records of scheduled drugs dispensed, but the majority of physicians do not access this information. To facilitate use by busy practitioners, most monitoring programs should improve access and response time, scan prescription data to flag suspicious purchasing patterns and alert physicians and pharmacists. Physicians could also prevent doctor shopping by adopting procedures to screen new patients for their risk of abuse and to monitor patients' adherence to prescribed treatments.

Cannabis Or Alcohol First? Differences By Ethnicity and In Risk For Rapid Progression To Cannabis-Related Problems In Women. Sartor CE, Agrawal A, Lynskey MT, Duncan AE, Grant JD, Nelson EC, Madden PAF, Heath AC, Bucholz KK. Psychol Med. 2013; 43 (4): 813-823.

Initiation of cannabis use typically follows alcohol use, but the reverse order does occur and is more common for African-Americans (AAs) than European-Americans (EAs). The aim of this study was to test for differences in the order of initiation of cannabis and alcohol use between AA and EA women and to determine whether order and ethnicity contribute independently to risk for rapid progression to cannabis-related problems. Data were drawn from structured psychiatric interviews of 4,102 women (mean age = 21.6 years), 3,787 from an all-female twin study and 315 from a high-risk family study; 18.1% self-identified as AA, 81.9% as EA. Ethnicity and order of initiation of cannabis and alcohol use were modeled as predictors of transition time from first use to onset of cannabis use disorder symptom(s) using Cox proportional hazards regression analyses. AA women were nearly three times as likely as EA women to initiate cannabis use before alcohol use. Using cannabis before alcohol [hazard ratio (HR) 1.44, 95% confidence interval (CI) 1.08-1.93] and AA ethnicity (HR 1.59, 95% CI 1.13-

2.24) were both associated with rapid progression from first use to cannabis symptom onset even after accounting for age at initiation and psychiatric risk factors. The findings indicate that AA women are at greater risk for rapid development of cannabis-related problems than EA women and that this risk is even higher when cannabis use is initiated before alcohol use. Prevention programs should be tailored to the various patterns of cannabis use and relative contributions of risk factors to the development of cannabis-related problems in different ethnic groups.

Alcohol Outlets and Binge Drinking In Urban Neighborhoods: The Implications Of Nonlinearity For Intervention and Policy. Ahern J, Margerison-Zilko C, Hubbard A, Galea S. Am J Public Health. 2013; 103(4): e81-87.
Alcohol outlet density has long been associated with alcohol-related harms, and policymakers have endorsed alcohol outlet restriction to reduce these harms. However, potential nonlinearity in the relation between outlet density and alcohol consumption has not been rigorously examined. The authors used data from the New York Social Environment Study (n = 4,000) to examine the shape of the relation between neighborhood alcohol outlet density and binge drinking by using a generalized additive model with locally weighted scatterplot smoothing, and applied an imputation-based marginal modeling approach. The authors found a nonlinear relation between alcohol outlet density and binge drinking; the association was stronger at densities of more than 80 outlets per square mile. Binge drinking prevalence was estimated to be 13% at 130 outlets, 8% at 80 outlets, and 8% at 20 outlets per square mile. This nonlinearity suggests that reductions in alcohol outlet density where density is highest and the association is strongest may have the largest public health impact per unit reduction. Future research should assess the impact of policies and interventions that aim to reduce alcohol outlet density, and consider nonlinearity in effects.

Assessment Of A Modified DSM-5 Diagnosis Of Alcohol Use Disorder In A Genetically Informative Population. Edwards AC, Gillespie NA, Aggen SH, Kendler KS. Alcohol Clin Exp Res. 2013; 37(3): 443-451.
Proposed changes to the upcoming DSM-5 include the following: (i) combining criteria for DSM-IV alcohol abuse (AA) and alcohol dependence (AD) into 1 diagnostic category (alcohol use disorder [AUD]); (ii) exclusion of the "legal problems" (LP) criterion; and (iii) addition of a "craving" criterion. Few published studies empirically assess the potential consequences of the proposed changes. Using a population-based sample of twins assessed for lifetime AA/AD diagnoses, the authors explored phenotypic differences across DSM-IV and a modified DSM-5 diagnoses without craving because of its unavailability in the data set. They used factor analysis and item response theory (IRT) to evaluate the potential consequences of excluding the LP criterion from AUD and used twin modeling to examine genetic differences between DSM-IV and the modified DSM-5 diagnoses. The prevalence of AUD was slightly higher than that of DSM-IV diagnoses. Individuals meeting DSM-IV, or DSM-5 criteria, but not both exhibit fewer comorbid diagnoses than those meeting both sets of criteria. Individuals meeting only DSM-5 criteria were slightly less severely affected than those meeting only DSM-IV criteria. Factor analysis indicated that the LP criterion loading is the lowest of all symptoms; IRT analysis suggested that this criterion has low discriminatory power. The genetic correlation between DSM-IV and DSM-5 diagnoses was slightly but significantly lower than unity. The proposed DSM-5 AUD criteria are unlikely to result in significant changes in

prevalence of diagnosed alcohol problems. However, it is unclear whether the new criteria represent a more valid diagnosis: new cases are no more severely affected than DSM-IV-only cases. Given the psychometric properties of LP, its exclusion should not negatively impact diagnostic validity. Similarly, the stable heritability across DSM-IV and DSM-5 diagnoses suggests that the proposed changes will not have substantial negative consequences in terms of familial influences, a key validator. These results provide equivocal empirical support for the proposed DSM-5 changes for AUDs.

Simultaneous Alcohol and Marijuana Use Among US High School Seniors From 1976 To 2011: Trends, Reasons, and Situations. Terry-McElrath YM, O'Malley PM, Johnston LD. DAD online 24 June 2013.

Simultaneous alcohol and marijuana (SAM) use raises significant concern due to the potential for additive or interactive psychopharmacological effects. However, no nationally representative studies are available that document prevalence, trends, or related factors in US youth SAM use. Nationally representative cross-sectional samples of 12th grade students surveyed in the Monitoring the Future project from 1976 to 2011 provided data on SAM use. Analyses were conducted in 2012. In 2011, 23% of all US high school seniors reported any SAM use. Among seniors reporting any past 12-month marijuana use, 62% reported any SAM use and 13% reported SAM use most or every time they used marijuana. SAM use consistently followed trends for past 30-day alcohol use over time. SAM use showed significant variation by psychosocial and demographic characteristics and was strongly associated with higher substance use levels, but occurred across the substance use spectrum. Certain reasons for alcohol or marijuana use (to increase effects of another drug; I'm hooked) and situations of alcohol or marijuana use (park/beach, car, party) were strongly associated with SAM use. The authors conclude that a sizable proportion of US high school seniors reported SAM use, and it appeared to occur frequently in social use situations that could impact both the public as well as youth drug users. SAM use appears to be a complex behavior that is incidental to general substance use patterns as well as associated with (a) specific simultaneous reasons (or expectancies), and (b) heavy substance use and perceived dependence, especially on alcohol.

Repeated Changes In Reported Sexual Orientation Identity Linked To Substance Use Behaviors In Youth. Ott MQ, Wypij D, Corliss HL, Rosario M, Reisner SL, Gordon AR, Austin SB. J Adolesc Health. 2013; 52(4): 465-472.

Previous studies have found that sexual minority (e.g., lesbian, gay, bisexual) adolescents are at higher risk of substance use than heterosexuals, but few have examined how changes in sexual orientation over time may relate to substance use. The authors examined the associations between change in sexual orientation identity and marijuana use, tobacco use, and binge drinking in U.S. youth. Prospective data from 10,515 U.S. youth ages 12-27 years in a longitudinal cohort study were analyzed using sexual orientation identity mobility measure M (frequency of change from 0 [no change] to 1 [change at every wave]) in up to five waves of data. Generalized estimating equations were used to estimate substance use risk ratios and 95% confidence intervals; interactions by sex and age group were assessed. All substance use behaviors varied significantly by sexual orientation. Sexual minorities were at higher risk for all outcomes, excluding binge drinking in males, and mobility score was positively associated with substance use in most cases ($p < .05$). The association between mobility and substance use remained significant after adjusting for current sexual orientation and varied by sex and

age for selected substance use behaviors. This association had a higher positive magnitude in females than males and in adolescents than young adults. In both clinical and research settings it is important to assess history of sexual orientation changes. Changes in reported sexual orientation over time may be as important as current sexual orientation for understanding adolescent substance use risk.

Situating HIV Risk In the Lives Of Formerly Trafficked Female Sex Workers On the Mexico-US Border. Collins SP, Goldenberg SM, Burke NJ, Bojorquez-Chapela IS, Jay G, Strathdee S. AIDS Care. 2013; 25(4): 459-465.
Due to stigma and the psychosocial repercussions of past trauma and abuse, survivors of sex trafficking may experience increased susceptibility to violence, revictimization, and various harmful health outcomes, including HIV infection. Given the paucity of research characterizing the experiences of formerly trafficked female sex workers (FSWs), the authors set out to describe and contextualize perceptions of HIV risk among women who have experienced past episodes of sex trafficking and who are currently engaged in sex work in Tijuana, Mexico. Based on semi-structured interviews and ethnographic fieldwork, the authors describe the following interrelated themes as influencing formerly trafficked FSWs' perceptions and experiences of HIV risk: economic vulnerability; susceptibility to violence; and psychological trauma. These findings highlight the need for HIV prevention efforts to incorporate broader structural and social interventions aimed at reducing vulnerability to violence and human rights abuses among this population and improving their general economic, psychological, and social well-being.

Alcohol Expectancies, Perceived Norms, and Drinking Behavior Among College Students: Examining the Reciprocal Determinism Hypothesis. Wardell JD, Read JP. Psychol Addict Behav. 2013; 27(1): 191-196.
Social learning mechanisms, such as descriptive norms for drinking behavior (norms) and positive alcohol expectancies (PAEs), play a major role in college student alcohol use. According to the principle of reciprocal determinism (Bandura, 1977), norms and PAEs should be reciprocally associated with alcohol use, each influencing one another over time. However, the nature of these prospective relationships for college students is in need of further investigation. This study provided the first examination of the unique reciprocal associations among norms, PAEs, and drinking together in a single model. PAEs become more stable with age, whereas norms are likely to be more dynamic upon college entry. Thus, the authors hypothesized that alcohol use would show stronger reciprocal associations with norms than with PAEs for college students. Students (N = 557; 67% women) completed online measures of PAEs, norms, and quantity and frequency of alcohol use in September of their first (T1), second (T2), and third (T3) years of college. Reciprocal associations were analyzed using a cross-lagged panel design. PAEs had unidirectional influences on frequency and quantity of alcohol use, with no prospective effects from alcohol use to PAEs. Reciprocal associations were observed between norms and alcohol use, but only for quantity and not for frequency. Specifically, drinking quantity prospectively predicted quantity norms and quantity norms prospectively predicted drinking quantity. This effect was observed across both years in the model. These findings support the reciprocal determinism hypothesis for norms but not for PAEs in college students and may help to inform norm-based interventions.

HIV/STI Risk Among Venue-Based Female Sex Workers Across The Globe: A Look Back and The Way Forward. Pitpitan EV, Kalichman SC, Eaton LA, Strathdee SA, Patterson TL. Curr HIV/AIDS Rep. 2013; 10 (1): 65-78.
Female sex workers (FSWs) continue to represent a high-risk population in need of targeted HIV prevention interventions. Targeting environmental risk factors should result in more sustainable behavior change than individual-level interventions alone. There are many types of FSWs who operate in and through a variety of micro- (e.g., brothels) and macro-level (eg, being sex-trafficked) contexts. Efforts to characterize FSWs and inform HIV prevention programs have often relied on sex work typologies or categorizations of FSWs by venue or type. The authors conducted a systematic search and qualitatively reviewed 37 published studies on venue-based FSWs to examine the appropriateness of sex work typologies, and the extent to which this research has systematically examined characteristics of different risk environments. They extracted information on study characteristics like venue comparisons, HIV/STI prevalence, and sampling strategies. They found mixed results with regards to the reliability of typologies in predicting HIV/STI infection; relying solely on categorization of FSWs by venue or type did not predict seroprevalence in a consistent manner. Only 65 % of the studies that allowed for venue comparisons on HIV/STI prevalence provided data on venue characteristics. The factors that were assessed were largely individual-level FSW factors (eg, demographics, number of clients per day), rather than social and structural characteristics of the risk environment. The authors outline a strategy for future research on venue-based FSWs that ultimately aims to inform structural-level HIV interventions for FSWs.

Epidemiologic Survey on Alcohol and Related Conditions. Blanco C, Krueger R, Hasin D, Liu S, Wang S, Kerridge B, Saha T, Olfson M. JAMA Psychiatry. 2013; 70(2): 199-208.
Clinical experience and factor analytic studies suggest that some psychiatric disorders may be more closely related to one another, as indicated by the frequency of their co-occurrence, which may have etiologic and treatment implications. The objective of this study was to construct a virtual space of common psychiatric disorders, spanned by factors reflecting major psychopathologic dimensions, and locate psychiatric disorders in that space, as well as to examine whether the location of disorders at baseline predicts the prevalence and incidence of disorders at 3-year follow-up. A total of 34,653 individuals participated in waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. The distance between disorders at wave 1, calculated using the loadings of the factors spanning the space of disorders as coordinates. This distance was correlated with the adjusted odds ratios for age, sex, and race/ethnicity of the prevalence and incidence of Axis I disorders in wave 2, with the aim of determining whether smaller distances between disorders at wave 1 predicts higher disorder prevalence and incidence at wave 2. A model with 3 correlated factors provided an excellent fit (Comparative Fit Index = 0.99, Tucker-Lewis Index = 0.98, root mean square error of approximation = 0.008) for the structure of common psychiatric disorders and was used to span the space of disorders. Distances ranged from 0.070 (between drug abuse and alcohol dependence) to 1.032 (between drug abuse and dysthymia). The correlation of distance between disorders in wave 1 with adjusted odds ratios of prevalence in wave 2 was -0.56. The correlation of distance in wave 1 with adjusted odds ratios of incidence in wave 2 was -0.57. The authors conclude that mapping psychiatric disorders can be used to quantify the distances among disorders. Proximity in turn can be used to predict prospectively the incidence and prevalence of Axis I disorders.

Gender Differences In Cannabis Use Disorders: Results From the National Epidemiologic Survey Of Alcohol and Related Conditions. Khan SS, Secades-Villa RO, Mayumi WS, Perez-Fuentes G, Kerridge BT, Blanco C. Drug Alcohol Depend. 2013; 130(1-3):101-108. The objective of this study was to examine gender differences among individuals diagnosed with DSM-IV lifetime cannabis use disorder (CUD). A nationally representative sample of U.S. adults aged 18 years or older that were diagnosed with lifetime CUD (n=3,297): Men (n=2,080), Women (n=1,217). Data were drawn from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43,093). The survey response rate was 81%.Nearly all individuals with CUD had a psychiatric comorbidity (95.6% of men, 94.1% of women). Men with lifetime CUD were more likely than women to be diagnosed with any psychiatric disorder, any substance use disorder and antisocial personality disorder, whereas women with CUD had more mood and anxiety disorders. After adjusting for gender differences in sociodemographic correlates and the prevalence of psychiatric disorders in the general population, women with CUD were at greater risk for externalizing disorders. Men with CUD met more criteria for cannabis abuse, had longer episodes of CUD, smoked more joints, and were older at remission when compared to women with CUD. Women experienced telescoping to CUD. Treatment-seeking rates were very low for both genders, and there were no gender differences in types of services used or reasons for not seeking treatment. There are important gender differences in the clinical characteristics and psychiatric comorbidities among individuals with CUD.

Prospective Associations Of Internalizing and Externalizing Problems and Their Co-Occurrence With Early Adolescent Substance Use. Colder CR, Scalco M, Trucco EM, Read JP, Lengua LJ, Wieczorek WF, Hawk, Jr. LW. J Abnorm Child Psychol. 2013; 41(4): 667-677.
The literature is equivocal regarding the role of internalizing problems in the etiology of adolescent substance use. In this study, the authors examined the association of internalizing and externalizing behavior problems and their co-occurrence with early adolescent substance use to help clarify whether internalizing problems operate as a risk or protective factor. A large community sample (N=387) mean age at the first assessment 12 years old; (83% White/non-Hispanic) was assessed annually for 3 years. Externalizing problem behavior in the absence of internalizing problems showed the strongest prospective association with alcohol, cigarette, and marijuana use. A weaker albeit statistically significant prospective positive association was found between co-occurring internalizing and externalizing behavior problems and substance use. Internalizing problems in the absence of externalizing problems protected adolescents against cigarette and marijuana use. Clarifying the role of internalizing problems in the etiology of adolescent substance use can inform the development of early intervention and prevention efforts. These results highlight the importance of further considering the co-occurrence of internalizing and externalizing behavior problems in developmental pathways to substance use.

Homelessness Independently Predicts Injection Drug Use Initiation Among Street-Involved Youth In A Canadian Setting. Feng C, DeBeck K, Kerr T, Mathias S, Montaner J, Wood, E. J Adolesc Health. 2013; 52(4): 499-501.
This longitudinal study examines the association between homelessness and injection drug use initiation among a cohort of street-involved youth in a setting of high-prevalence crystal

methamphetamine use. The authors derived data from the At-Risk Youth Study, a prospective cohort of street-involved youth aged 14-26 years, recruited between September 2005 and November 2011. They used Cox proportional hazards regression to identify factors independently associated with time to injection initiation. Among 422 street-youth who had never injected at baseline, the authors observed 77 injection initiation events during follow-up. Homelessness was independently associated with injection initiation in multivariate Cox regression (relative hazard, 1.80 [95% confidence interval, 1.13-2.87]) after adjusting for crystal methamphetamine use and other potential confounders. These findings highlight that homelessness is a key risk factor for injection initiation among street-involved youth. Supportive housing interventions for street youth may help prevent injection drug use initiation within this high-risk population.

Probability and Predictors Of Treatment-Seeking For Prescription Opioid Use Disorders: A National Study. Blanco C, Iza M, Schwartz RP, Rafful C, Wang S, Olfson M. Drug Alcohol Depend. 2013; 131 (1-2): 143-148.
Prescription opioid use disorders are the second most common drug use disorder behind only cannabis use disorders. Despite this, very little is known about the help-seeking behavior among individuals with these disorders. The sample included respondents of the Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) with a lifetime diagnosis of prescription drug use disorders (N=623). Unadjusted and adjusted hazard ratios are presented for time to first treatment-seeking by sociodemographic characteristics and comorbid psychiatric disorders. The lifetime cumulative probability of treatment seeking was 42% and the median delay from prescription drug use disorder onset to first treatment was 3.83 years. Having an earlier onset of prescription opioid use disorder and a history of bipolar disorder, major depression disorder, specific phobia and cluster B personality disorders predicted shorter delays to treatment. Although some comorbid psychiatric disorders increase the rate of treatment-seeking and decrease delays to first-treatment contact rates of treatment-seeking for prescription drug use disorder are low, even when compared with rates of treatment for other substance use disorders. Given the high prevalence and adverse consequences of prescription drug use disorder, there is a need to improve detection and treatment of prescription opioid use disorder.

Childhood Sexual Abuse and Early Substance Use In Adolescent Girls: The Role Of Familial Influences. Sartor CE, Waldron MD, Alexis E, Grant JD, McCutcheon VV, Nelson EC, Madden PAF, Bucholz KK, Heath AC. Addiction. 2013; 108(5): 993-1000.
The aim of this study was to assess the extent to which the association between childhood sexual abuse (CSA) and early use of alcohol, cigarettes and cannabis in adolescent girls is mediated by risk factors that tend to cluster in families where CSA occurs. An abridged version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) was administered by telephone. A total of 3,761 female twins aged 18-29 (14.6% African American, 85.4% European American). CSA experiences and history of substance use were queried in the SSAGA-based interviews. After controlling for familial influences on early substance use by including co-twin early use status in models, separate Cox proportional hazards regression analyses predicting onset of alcohol, cigarette and cannabis use revealed a significant association with CSA. The effect was observed to age 19 years for cigarettes and to age 21 years for cannabis, but was limited to age 14 years or younger for alcohol, with the

most pronounced risk before age 10 [hazard ratio (HR) =4.59; confidence interval (CI): 1.96-10.74]. CSA-associated risk for initiation of cigarette and cannabis use was also highest in the youngest age range, but the decline with age was much more gradual and the hazard ratios significantly lower (HR: 1.70; CI: 1.13-2.56 for cigarettes and HR: 2.34, CI: 1.57-3.48 for cannabis). Childhood sexual abuse history is a distinct risk factor for use of cigarettes and cannabis, and a very strong predictor of early age at first drink.

Three Mutually Informative Ways To Understand the Genetic Relationships Among Behavioral Disinhibition, Alcohol Use, Drug Use, Nicotine Use/Dependence, and Their Co-Occurrence: Twin Biometry, GCTA, and Genome-Wide Scoring. Vrieze SI, McGue M, Miller MB, Hicks BM, Iacono WG. Behav Genet. 2013; 43(2): 97-107.
Behavioral disinhibition is a trait hypothesized to represent a general vulnerability to the development of substance use disorders. The authors used a large community-representative sample (N = 7,188) to investigate the genetic and environmental relationships among measures of behavioral disinhibition, Nicotine Use/Dependence, Alcohol Consumption, Alcohol Dependence, and Drug Use. First, using a subsample of twins (N = 2,877), they used standard twin models to estimate the additive genetic, shared environmental, and non-shared environmental contributions to these five traits. Heritabilities ranged from .42 to .58 and shared environmental effects ranged from .12 to .24. Phenotypic correlations among the five traits were largely attributable to shared genetic effects. Second, the authors used Genome-wide Complex Trait Analysis (GCTA) to estimate as a random effect the aggregate genetic effect attributable to 515,384 common SNPs. The aggregated SNPs explained 10-30 % of the variance in the traits. Third, a genome-wide scoring approach summed the actual SNPs, creating a SNP-based genetic risk score for each individual. After tenfold internal cross-validation, the SNP sumscore correlated with the traits at .03 to .07 ($p < .05$), indicating small but detectable effects. SNP sumscores generated on one trait correlated at approximately the same magnitude with other traits, indicating detectable pleiotropic effects among these traits. Behavioral disinhibition thus shares genetic etiology with measures of substance use, and this relationship is detectable at the level of measured genomic variation.

Predictors Of Quit Attempts and Successful Quit Attempts In A Nationally Representative Sample Of Smokers. Rafful C, Garcia-Rodriguez OW, Shuai Secades-Villa R, Martinez-Ortega JM, Blanco, C. Addict Behav. 2013; 38(4): 1920-1923.
Although most current smokers report that they would like to quit, most quit attempts fail suggesting that predictors of quitting attempts may differ from those of successful attempts. The authors examined sociodemographic and clinical predictors of quit attempts and successful quit attempts in a nationally representative sample of US adults. Data was collected in 2001-2002 (Wave 1) and 2004-2005 (Wave 2). Almost 40% of individuals who had not previously attempted to quit, tried to quit over the next three years; only 4.6% of those who tried had succeeded at the time of the evaluation. Hispanics, Asians, individuals with high income, and those with college education were less likely to attempt to quit, whereas those with daily nicotine use, younger age at first use and most symptoms of dependence were more likely to do so. Having an educational level below high school and older age at first nicotine use were predictors of successful quitting. Despite relatively high rates of quit attempts, rates of success are extremely low, indicating a gap between the public health need of decreasing tobacco use, and existing means to achieve it. Although there is a need to encourage people to

quit tobacco, there may be an equally large need to develop more effective interventions that increase the rate of successful quit attempts.

The Impact Of Substance Use, Sexual Trauma, and Intimate Partner Violence On Sexual Risk Intervention Outcomes In Couples: A Randomized Trial. Few HIV prevention interventions focus on sexual risk reduction as mutual process determined by couple members, though risk behaviors are inter-dependent. This trial examined the impact of substance use, history of sexual trauma, and intimate partner violence on sexual risk associated with participation in a risk reduction intervention. HIV seroconcordant and serodiscordant multicultural couples in Miami, Florida (n=216) were randomized to group (n=112) or individual (n=104) couple-based interventions. Group intervention participants increased condom use in couples in which women had a history of sexual trauma [F(2,221)=3.39, p=0.036] and by partners of alcohol users. History of sexual trauma was a determinant of conflict resolution, predicting negative communication and intimate partner violence. Results emphasize the need for group sexual risk reduction interventions targeting sexual trauma, partner violence, and substance use among HIV seroconcordant and serodiscordant couples. Jones DL, Kashy DV, Olga M, Cook R, Weiss SM. Ann Behav Med. 2013; 45(3): 318-328.

Acceptability Of Vaginal Microbicides Among Female Sex Workers and Their Intimate Male Partners In Two Mexico-US Border Cities: A Mixed Methods Analysis. Robertson AM, Syvertsen JL, Martinez G, Rangel MG, Palinkas LA, Stockman JK, Ulibarri MD, Strathdee SA. Glob Public Health. 2013; 8(5): 619-633.
Female sex workers (FSWs) may benefit from pre-exposure prophylaxis (PrEP) including microbicides for HIV prevention. Since adherence is a key factor in PrEP efficacy, the authors explored microbicide acceptability and potential barriers to use within FSWs' intimate relationships in Tijuana and Ciudad Juarez, Mexico, where HIV prevalence is increasing. FSWs and their verified intimate (non-commercial) male partners completed quantitative and qualitative interviews from 2010 to 2012. The authors' complementary mixed methods design followed an iterative process to assess microbicide acceptability, explore related relationship dynamics and identify factors associated with concern about male partners' anger regarding microbicide use. Among 185 couples (n=370 individuals), interest in microbicides was high. In qualitative interviews with 28 couples, most participants were enthusiastic about microbicides for sex work contexts but some explained that microbicides could imply mistrust/infidelity within their intimate relationships. In the overall sample, nearly one in six participants (16%) worried that male partners would become angry about microbicides, which was associated with higher self-esteem among FSWs and lower self-esteem and past year conflicts causing injury within relationships among men. HIV prevention interventions should consider intimate relationship dynamics posing potential barriers to PrEP acceptability and adherence, involve male partners and promote risk communication skills.

Social and Generalized Anxiety Symptoms and Alcohol and Cigarette Use In Early Adolescence: The Moderating Role Of Perceived Peer Norms. Zehe JM, Colder CR, Read JP, Wieczorek WF, Lengua LJ. Addict Behav. 2013; 38(4): 1931-1939.
This study prospectively examines the association between social and generalized anxiety symptoms and alcohol and cigarette use in early adolescence and how injunctive (perceived peer approval of use) and descriptive (perceived peer use) norms may moderate the

association. Sex differences were also examined. Data were taken from a longitudinal study investigating problem behavior and adolescent substance use. The community sample (N=387) was assessed annually, and data from the first two waves of assessment were used for this study. Early adolescents were between the ages of 11 and 13 at the first assessment (mean age=11.05, SD=0.55, 55% female). Peer norms moderated the association between both social and generalized anxiety symptoms and the likelihood of alcohol and cigarette use for girls, but not for boys. Specifically, girls with elevated levels of generalized anxiety symptoms were at risk for use when perceived peer use was low, and protected from use when perceived peer use was high. Girls with elevated levels of social anxiety symptoms were at risk for use when perceived peer approval of use was high, and protected from use when perceived peer approval of use was low. Past studies have found inconsistent support for an association between anxiety and adolescent substance use, and these findings provide some clarity regarding for whom and when anxiety operates as a risk/protective factor. Social context and sex are critical for understanding the role of different forms of anxiety in the etiology of adolescent alcohol and cigarette use.

Social Support and Recovery Among Mexican Female Sex Workers Who Inject Drugs. Hiller SP, Syvertsen JL, Lozada R, Ojeda VD. J Subst Abuse Treat. 2013; 45(1): 44-54.
This qualitative study describes social support that female sex workers who inject drugs (FSW-IDUs) receive and recovery efforts in the context of relationships with family and intimate partners. The authors conducted thematic analysis of in-depth interviews with 47 FSW-IDUs enrolled in an intervention study to reduce injection/sexual risk behaviors in Tijuana, Mexico. FSW-IDUs received instrumental and emotional social support, which positively and negatively influenced recovery efforts. Participants reported how some intimate partners provided conflicting positive and negative support during recovery attempts. Problematic support (i.e., well-intended support with unintended consequences) occurred in strained family relationships, limiting the positive effects of support. Mexican drug treatment programs should consider addressing social support in recovery curricula through evidence-based interventions that engage intimate partners, children and family to better reflect socio-cultural and contextual determinants of substance abuse.

Interdisciplinary Mixed Methods Research With Structurally Vulnerable Populations: Case Studies Of Injection Drug Users In San Francisco. Lopez AM, Bourgois P, Wenger LD, Lorvick J, Martinez AN, Kral AH. Int J Drug Policy. 2013; 24(2):101-109.
Research with injection drug users (IDUs) benefits from interdisciplinary theoretical and methodological innovation because drug use is illegal, socially sanctioned and often hidden. Despite the increasing visibility of interdisciplinary, mixed methods research projects with IDUs, qualitative components are often subordinated to quantitative approaches and page restrictions in top addiction journals limit detailed reports of complex data collection and analysis logistics, thus minimizing the fuller scientific potential of genuine mixed methods. The authors present the methodological logistics and conceptual approaches of four mixed-methods research projects that their interdisciplinary team conducted in San Francisco with IDUs over the past two decades. These projects include combinations of participant-observation ethnography, in-depth qualitative interviewing, epidemiological surveys, photo-documentation, and geographic mapping. The authors adapted Greene et al.'s framework for combining methods in a single research project through: data triangulation, methodological

complementarity, methodological initiation, and methodological expansion. They argue that: (1) flexible and self-reflexive methodological procedures allowed them to seize strategic opportunities to document unexpected and sometimes contradictory findings as they emerged to generate new research questions, (2) iteratively mixing methods increased the scope, reliability, and generalizability of these data, and (3) interdisciplinary collaboration contributed to a scientific "value added" that allowed for more robust theoretical and practical findings about drug use and risk-taking.

Early Smoking Onset and Risk For Subsequent Nicotine Dependence: A Monozygotic Co-Twin Control Study. Kendler KS, Myers J, Damaj MI, Chen X. Am J Psychiatry. 2013; 170(4): 408-413.

Early onset of regular smoking is associated with an elevated risk for later nicotine dependence. Whether or not this association is causal is unknown and has substantial public policy implications. The authors used a monozygotic co-twin control study design. Pairs were selected from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders for discordance in age at onset of regular smoking. Nicotine dependence was measured by the Fagerstrom test for nicotine dependence and level of craving. The authors identified 175 male-male and 69 female-female monozygotic twin pairs who differed by at least 2 years in age at onset of regular smoking. During their period of heaviest smoking, the twin who began smoking earlier had significantly higher Fagerstrom test scores in both the male-male (Cohen's d=0.20) and female-female twin pairs (d=0.26). Craving for cigarettes when unable to smoke was also higher in the early-onset member in both groups (male pairs, d=0.38; female pairs, d=0.25). The early-onset smoking twin did not differ from the later-onset twin in symptoms of alcohol or cannabis abuse or dependence, current alcohol use, or maximal level of cannabis, sedative, stimulant, or cocaine use. Controlling for genetic and familial-environmental effects, age at onset of regular smoking predicted level of nicotine dependence. Consistent with the animal literature, these findings suggest that in humans, early nicotine exposure directly increases level of later nicotine dependence. These results should be interpreted in the context of the methodological strengths and limitations of the monozygotic co-twin design.

'In Different Situations, In Different Ways': Male Sex Work In St. Petersburg, Russia. Niccolai LM, King EJ, Eritsyan KU, Safiullina L, Rusakova M M. Cult Health Sex. 2013; 15(4): 480-493.

The authors conducted a qualitative study of male sex work in St. Petersburg Russia with a focus on social vulnerabilities, HIV-risk perception and HIV-related behaviours. In-depth interviews were conducted with individuals knowledgeable about male sex work through their profession and with male sex workers themselves. Male sex work involves a variety of exchanges, including expensive vacations, negotiated monetary amounts or simply access to food. Methods of finding clients included the Internet, social venues (e.g. gay clubs and bars) and public places (e.g. parks). Use of the Internet greatly facilitated male sex work in a variety of ways. It was used by both individuals and agencies to find clients, and appeared to be increasing. Men often reported not being professionally connected to other male sex workers and limited disclosure about their work. Many were aware of the work-related risks to personal safety, including violence and robbery by clients. Perceived risk for HIV was mostly abstract and several exceptions to condom use with clients were noted. Alcohol use was reported as

moderate but alcohol was consumed frequently in association with work. These data suggest that the most salient risks for male sex workers include professional isolation, threats to personal safety, limited perceived HIV risk and sub-optimal levels of condom use.

Genes, Environments, and Developmental Research: Methods For A Multi-Site Study Of Early Substance Abuse. Costello EJ, Eaves L, Sullivan P, Kennedy M, Conway Kevin, Adkins DE, Angold A, Clark SL, Erkanli A, McClay JL, Copeland W, Maes HH, Liu Y, Patkar AA, Silberg J, van den Oord E. Twin Res Hum Genet. 2013; 16(2): 505-515.
The importance of including developmental and environmental measures in genetic studies of human pathology is widely acknowledged, but few empirical studies have been published. Barriers include the need for longitudinal studies that cover relevant developmental stages and for samples large enough to deal with the challenge of testing gene-environment-development interaction. A solution to some of these problems is to bring together existing data sets that have the necessary characteristics. As part of the National Institute on Drug Abuse-funded Gene-Environment-Development Initiative, the authors' goal is to identify exactly which genes, which environments, and which developmental transitions together predict the development of drug use and misuse. Four data sets were used of which common characteristics include (1) general population samples, including males and females; (2) repeated measures across adolescence and young adulthood; (3) assessment of nicotine, alcohol, and cannabis use and addiction; (4) measures of family and environmental risk; and (5) consent for genotyping DNA from blood or saliva. After quality controls, 2,962 individuals provided over 15,000 total observations. In the first gene-environment analyses, of alcohol misuse and stressful life events, some significant gene-environment and gene-development effects were identified. The authors conclude that in some circumstances, already collected data sets can be combined for gene-environment and gene-development analyses. This greatly reduces the cost and time needed for this type of research. However, care must be taken to ensure careful matching across studies and variables.

Personality Dimensions as Common and Broadband-Specific Features for Internalizing and Externalizing Disorders. Hink LK, Rhee SH, Corley RP, Cosgrove VE, Hewitt JK, Schulz-Heik RJ, Lahey BB, Waldman ID. J Abnorm Child Psychol. 2013.
Several researchers have suggested that the nature of the covariation between internalizing and externalizing disorders may be understood better by examining the associations between temperament or personality and these disorders. The present study examined neuroticism as a potential common feature underlying both internalizing and externalizing disorders and novelty seeking as a potential broad-band specific feature influencing externalizing disorders alone. Participants were 12- to 18-year-old twin pairs (635 monozygotic twin pairs and 691 dizygotic twin pairs; 48% male and 52% female) recruited from the Colorado Center for Antisocial Drug Dependence. Genetic and nonshared environmental influences shared in common with neuroticism influenced the covariation among distinct internalizing disorders, the covariation among distinct externalizing disorders, and the covariation between internalizing and externalizing disorders. Genetic influences shared in common with novelty seeking influenced the covariation among externalizing disorders and the covariation between major depressive disorder and externalizing disorders, but not the covariation among internalizing disorders or between anxiety disorders and externalizing disorders. Also, after accounting for genetic and environmental influences shared in common with neuroticism and

novelty seeking, there were no significant common genetic or environmental influences among the disorders examined, suggesting that the covariance among the disorders is sufficiently explained by neuroticism and novelty seeking. The authors conclude that neuroticism is a heritable common feature of both internalizing disorders and externalizing disorders, and that novelty seeking is a heritable broad-band specific factor that distinguishes anxiety disorders from externalizing disorders.

Where and When Adolescents Use Tobacco, Alcohol, and Marijuana: Comparisons By Age, Gender, and Race. Goncy EA, Mrug S. J Stud Alcohol Drugs. 2013; 74(2): 288-300.
This study examined the location and time of adolescent use of cigarettes, alcohol, and marijuana. Age, gender, and racial differences in location and time of use were studied for each substance. Using cross-sectional data collected through the school wide Pride Survey, 20,055 students between the ages of 10 and 19 years (53.6% female, 55.1% Black, 44.9% White) in one metropolitan area reported on their frequency of cigarette, alcohol, and marijuana use, as well as the location and time of use of each substance. Chi-square tests compared the rates, locations, and times for each substance across boys and girls; Black and White students; and early, middle, and late adolescents. Older adolescents reported higher rates of substance use at friends' homes, at school, and in cars and lower rates of alcohol use at home compared with younger youth. Males were more likely to report alcohol and marijuana use at school and on weeknights and alcohol use in cars, whereas females were more likely to report alcohol and marijuana use on the weekends. No gender differences emerged for times and locations of cigarette use. Compared with Black youth, White adolescents were more likely to use all substances at friends' homes and on weekends; to smoke cigarettes at school, in the car, and on weeknights; and to use alcohol at home. Black adolescents were more likely to report using alcohol at home, at school, in cars, during and after school, and on weeknights and were more likely to report using marijuana at school. The location and time of adolescent substance use vary substantially by age, gender, and race. These differences may help tailor substance use prevention and intervention programs to specific subgroups of youth to improve program effectiveness.

Alcoholism and Timing Of Separation In Parents: Findings In A Midwestern Birth Cohort. Waldron M, Bucholz KK, Lynskey MT, Madden PAF, Heath AC. J Stud Alcohol Drugs. 2013; 74(2): 337-348.
The authors examined history of alcoholism and occurrence and timing of separation in parents of a female twin cohort. Parental separation (never-together; never-married cohabitants who separated; married who separated) was predicted from maternal and paternal alcoholism in 326 African ancestry (AA) and 1,849 European/ other ancestry (EA) families. Broad (single-informant, reported in abstract) and narrow (self-report or two-informant) measures of alcoholism were compared. Parental separation was more common in families with parental alcoholism: By the time twins were 18 years of age, parents had separated in only 24% of EA families in which neither parent was alcoholic, contrasted with 58% of families in which only the father was (father-only), 61% of families in which only the mother was (mother-only), and 75% in which both parents were alcoholic (two-parent); corresponding AA percentages were 59%, 71%, 82%, and 86%, respectively. Maternal alcoholism was more common in EA never together couples (mother-only: odds ratio [OR] = 5.95; two parent: OR = 3.69). In ever-together couples, alcoholism in either parent predicted elevated risk of separation, with half of

EA relationships ending in separation within 12 years of twins' birth for father-only families, 9 years for mother-only families, and 4 years for both parents alcoholic; corresponding median survival times for AA couples were 9, 4, and 2 years, respectively. EA maternal alcoholism was especially strongly associated with separation in the early postnatal years (mother-only: birth-5 years, hazard ratio [HR] = 4.43; 6 years on, HR = 2.52; two-parent: HRs = 5.76, 3.68, respectively). Parental separation is a childhood environmental exposure that is more common in children of alcoholics, with timing of separation highly dependent on alcoholic parent gender.

An Epidemiologic Update On Hepatitis C Infection In Persons Living With Or At Risk Of HIV Infection. Kim AY, Onofrey S, Church DR. J Infect Dis. 2013; 207 Suppl 1: S1-6.
Due to shared routes of transmission, coinfection with both human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) is relatively common and results in accelerated liver disease, driving morbidity and mortality. Deaths related to HCV now exceed deaths related to HIV in the United States, and co-infected patients bear a significant proportion of that mortality. This burden may be addressed by novel antiviral therapies that promise increased rates of cure or by enhanced access to liver transplantation, but these are costly interventions. Ultimately, the future burden of coinfection is addressed by greater understanding of who is at risk for development of each infection, thus guiding preventive efforts. Key recent reports regarding the US burden of morbidity and mortality due to HCV and groups at risk for coinfection are reviewed, with a focus on recently described HCV occurring among young injection drug users and men who have sex with men. Given the lack of available vaccine against HCV, enhanced detection and surveillance is a vital component of our public health strategy to combat HCV.

Low-Frequency Heroin Injection Among Out-Of-Treatment, Street-Recruited Injection Drug Users. Harris JL, Lorvick J, Wenger L, Wilkins T, Iguchi MY, Bourgois PK, Alex H. J Urban Health. 2013; 90(2): 299-306.
In this paper, the authors explore the understudied phenomenon of "low-frequency" heroin injection in a sample of street-recruited heroin injectors not in drug treatment. They conducted a cross-sectional study of 2,410 active injection drug users (IDUs) recruited in San Francisco, California from 2000 to 2005. They compare the sociodemographic characteristics and injection risk behaviors of low-frequency heroin injectors (low-FHI; one to 10 self-reported heroin injections in the past 30days) to high-frequency heroin injectors (high-FHI; 30 or more self-reported heroin injections in the past 30days). Fifteen percent of the sample met criteria for low-FHI. African American race, men who have sex with men (MSM) behavior, and injection and noninjection methamphetamine use were independently associated with low-FHI. Compared to high-FHI, low-FHI were less likely to report syringe sharing and nonfatal heroin overdose. A small but significant proportion of heroin injectors inject heroin 10 or less times per month. Additional research is needed to qualitatively examine low-frequency heroin injection and its relationship to drug use trajectories.

Individual and Neighborhood Correlates Of Membership In Drug Using Networks With A Higher Prevalence Of HIV In New York City (2006-2009). Rudolph AE, Crawford ND, Latkin C, Fowler JH, Fuller CM. Ann Epidemiol. 2013; 23(5): 267-274.
To identify individual- and neighborhood-level correlates of membership within high HIV prevalence drug networks. The authors recruited 378 New York City drug users via respondent-driven sampling (2006-2009). Individual-level characteristics and recruiter-recruit relationships were ascertained and merged with 2000 tract-level U.S. Census data. Descriptive statistics and population average models were used to identify correlates of membership in high HIV prevalence drug networks (>10.54% vs. <10.54% HIV). Individuals in high HIV prevalence drug networks were more likely to be recruited in neighborhoods with greater inequality (adjusted odds ratio [AOR], 5.85; 95% confidence interval [CI], 1.40-24.42), higher valued owner-occupied housing (AOR, 1.48; 95% CI, 1.14-1.92), and a higher proportion of Latinos (AOR, 1.83; 95% CI, 1.19-2.80). They reported more crack use (AOR, 7.23; 95% CI, 2.43-21.55), exchange sex (AOR, 1.82; 95% CI, 1.03-3.23), and recent drug treatment enrollment (AOR, 1.62; 95% CI, 1.05-2.50) and were less likely to report cocaine use (AOR, 0.40; 95% CI, 0.20-0.79) and recent homelessness (AOR, 0.32; 95% CI, 0.17-0.57). The relationship between exchange sex, crack use, and membership within high HIV prevalence drug networks may suggest an ideal HIV risk target population for intervention. Coupling network-based interventions with those adding risk-reduction and HIV testing/care/adherence counseling services to the standard of care in drug treatment programs should be explored in neighborhoods with increased inequality, higher valued owner-occupied housing, and a greater proportion of Latinos.

Differentially Regulated Gene Expression Associated With Hepatitis C Virus Clearance. Grimes CZ, Hwang LY, Wei P, Shah DP, Volcik KA, Brown EL. J Gen Virol. 2013; 94(Pt 3): 534-542.
Human chronic hepatitis C virus (HCV) infections pose a significant public health threat, necessitating the development of novel treatments and vaccines. HCV infections range from spontaneous resolution to end-stage liver disease. Approximately 10-30% of HCV infections undergo spontaneous resolution independent of treatment by yet-to-be-defined mechanisms. These individuals test positive for anti-HCV antibodies in the absence of detectable viral serum RNA. To identify genes associated with HCV clearance, this study compared gene expression profiles between current drug users chronically infected with HCV and drug users who cleared their HCV infection. This analysis identified 91 differentially regulated (up- or down regulated by twofold or more) genes potentially associated with HCV clearance. The majority of genes identified were associated with immune function, with the remaining genes categorized either as cancer related or 'other'. Identification of factors and pathways that may influence virus clearance will be essential to the development of novel treatment strategies.

Individual- and Community-Level Correlates Of Cigarette-Smoking Trajectories From Age 13 To 32 In A U.S. Population-Based Sample. Fuemmeler B, Lee C-T, Ranby KW, Clark T, McClernon FJ, Yang C, Kollins SH. Drug Alcohol Depend. 2013.
Characterizing smoking behavior is important for informing etiologic models and targeting prevention efforts. This study explored the effects of both individual- and community-level variables in predicting cigarette use vs. non-use and level of use among adolescents as they transition into adulthood. Data on 14,779 youths (53% female) were drawn from the National

Longitudinal Study of Adolescent Health (Add Health); a nationally representative longitudinal cohort. A cohort sequential design allowed for examining trajectories of smoking typologies from age 13 to 32 years. Smoking trajectories were evaluated by using a zero-inflated Poisson (ZIP) latent growth analysis and latent class growth analysis modeling approach. Significant relationships emerged between both individual- and community-level variables and smoking outcomes. Maternal and peer smoking predicted increases in smoking over development and were associated with a greater likelihood of belonging to any of the four identified smoking groups versus Non-Users. Conduct problems and depressive symptoms during adolescence were related to cigarette use versus non-use. State-level prevalence of adolescent smoking was related to greater cigarette use during adolescence. The authors conclude that individual- and community-level variables that distinguish smoking patterns within the population aid in understanding cigarette use versus non-use and the quantity of cigarette use into adulthood. These findings suggest that efforts to prevent cigarette use would benefit from attention to both parental and peer smoking and individual well-being. Future work is needed to better understand the role of variables in the context of multiple levels (individual and community-level) on smoking trajectories.

Analyzing Repeated Measures Data On Individuals Nested Within Groups: Accounting For Dynamic Group Effects. Bauer DJ, Gottfredson NC, Dean D, Zucker RA. Psychol Methods. 2013; 18(1): 1-14.

Researchers commonly collect repeated measures on individuals nested within groups such as students within schools, patients within treatment groups, or siblings within families. Often, it is most appropriate to conceptualize such groups as dynamic entities, potentially undergoing stochastic structural and/or functional changes over time. For instance, as a student progresses through school, more senior students matriculate while more junior students enroll, administrators and teachers may turn over, and curricular changes may be introduced. What it means to be a student within that school may thus differ from 1 year to the next. This article demonstrates how to use multilevel linear models to recover time-varying group effects when analyzing repeated measures data on individuals nested within groups that evolve over time. Two examples are provided. The 1st example examines school effects on the science achievement trajectories of students, allowing for changes in school effects over time. The 2nd example concerns dynamic family effects on individual trajectories of externalizing behavior and depression.

HIV and Syphilis Infection Among Men Attending An Sexually Transmitted Infection Clinic In Puerto Rico. Colon-Lopez V, Ortiz AP, Banerjee G, Gertz AM, Garcia H. P R Health Sci J. 2013; 32(1): 8-13.

This study aimed to assess the demographic, behavioral, and clinical factors associated with HIV and syphilis infection among a sample of men attending a sexually transmitted infection clinic during 2009 to 2010 in San Juan, Puerto Rico (PR).A sample of 350 clinical records from men visiting the clinic for the first time during 2009 to 2010 was reviewed. Descriptive statistics were used to describe the study sample, and bivariate analyses were performed separately for HIV and syphilis to identify factors associated with these infectious diseases. Variables that were significantly associated ($p < 0.05$) with HIV and syphilis in the bivariate analysis were considered for inclusion in the logistic regression models. Overall, 11.2% and 14.1% of the men were infected with HIV and syphilis, respectively, and 5.1% were coinfected

with HIV and syphilis. In multivariate logistic regression models, ever injecting drugs (POR = 8.1; 95% CI 3.0, 21.8) and being a man who has sex with men (MSM) (POR = 5.3; 95% CI 2.3, 11.9) were positively associated with HIV infection. Being a man older than 45 years (POR = 4.0; 95% CI: 1.9, 8.9) and being an MSM (POR = 2.5; 95% CI: 1.3, 4.9) were both significantly associated with syphilis infection. These findings reinforce the need for greater education and prevention efforts for HIV and other STIs among men in PR, particularly those who are MSM. However, there is a need to make an a priori assessment of the level of health literacy in the members of this group so that a culturally sensitive intervention can be provided to the men who attend this STI clinic.

Determinants Of Hepatitis C Virus Treatment Completion and Efficacy In Drug Users Assessed By Meta-Analysis. Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Clin Infect Dis. 2013; 56(6): 806-816.
Hepatitis C virus (HCV)-infected drug users (DUs) have largely been excluded from HCV care. The authors conducted a systematic review and meta-analysis of the literature on treatment completion and sustained virologic response (SVR) rates in DUs. They assessed the effects of different treatment approaches and services to promote HCV care among DUs as well as demographic and viral characteristics. Studies of at least 10 DUs treated with pegylated interferon/ribavirin that reported SVR were analyzed. Heterogeneity was assessed (Cochran test) and investigated (meta-regression), and pooled rates were estimated (random effects).Thirty-six studies comprising 2866 patients were retrieved. The treatment completion rate among DUs was 83.4% (95% confidence interval [CI], 77.1%-88.9%). Among studies that included addiction-treated and untreated patients during HCV therapy, the higher the proportion of addiction-treated patients, the higher the HCV treatment completion rate ($P < .0001$). After adjusting for human immunodeficiency virus (HIV)/HCV coinfection, sex, and treatment of addiction, support services during antiviral therapy increased treatment completion ($P < .0001$). The pooled SVR rate was 55.5% (95% CI, 50.6%-60.3%). Genotype 1/4 ($P = .0012$) and the proportion of HIV-coinfected DUs ($P = .0173$) influenced the SVR rate. After adjusting for HCV genotype 1/4 and HIV/HCV coinfection, the SVR rate was positively correlated with involvement of a multidisciplinary team ($P < .0001$).Treatment of addiction during HCV therapy results in higher treatment completion. The authors' pooled SVR rate is similar to that obtained in registration trials in the general population. Treatment of addiction during HCV therapy will likely be important for HCV-infected DUs undergoing treatment with more complex regimens including direct-acting antivirals.

North American Indigenous Adolescent Substance Use. Walls M, Sittner H, Kelley J, Whitbeck LB. Addict Behav. 2013; 38(5): 2103-2109.
The aim of this study was to investigate growth in problem drinking and monthly marijuana use among North American Indigenous adolescents from the upper Midwest and Canada. Panel data from a community-based participatory research project includes responses from 619 adolescents residing on or near 7 different reservations/reserves. All respondents were members of the same Indigenous cultural group. Rates of problem drinking and monthly marijuana use increased steadily across the adolescent years, with fastest growth occurring in early adolescence (before age 15). In general, female participants reported higher rates of substance use prior to age 15; however, male reports of use surpassed those of females in later

adolescence. Results of this study highlight the importance of early adolescent substance use prevention efforts and the possible utility of gender responsive programming.

The Onset Of STI Diagnosis Through Age 30: Results From the Seattle Social Development Project Intervention. Hill KG, Bailey JA, Hawkins JD, Catalano RF, Kosterman R, Oesterle S, Abbott RD. Prev Sci. 2013.
The objectives of this study were to examine (1) whether the onset of sexually transmitted infections (STI) through age 30 differed for youths who received a social developmental intervention during elementary grades compared to those in the control condition; (2) potential social-developmental mediators of this intervention; and (3) the extent to which these results differed by ethnicity. A nonrandomized controlled trial followed participants to age 30, 18 years after the intervention ended. Three intervention conditions were compared: a full-intervention group, assigned to intervention in grades 1 through 6; a late intervention group, assigned to intervention in grades 5 and 6 only; and a no-treatment control group. Eighteen public elementary schools serving diverse neighborhoods including high-crime neighborhoods of Seattle are the setting of the study. Six hundred eight participants in three intervention conditions were interviewed from age 10 through 30. Interventions include teacher training in classroom instruction and management, child social and emotional skill development, and parent workshops. Outcome is the cumulative onset of participant report of STI diagnosis. Adolescent family environment, bonding to school, antisocial peer affiliation, early sex initiation, alcohol use, cigarette use, and marijuana use were tested as potential intervention mechanisms. Complementary log-log survival analysis found significantly lower odds of STI onset for the full-intervention compared to the control condition. The lowering of STI onset risk was significantly greater for African Americans and Asian Americans compared to European Americans. Family environment, school bonding, and delayed initiation of sexual behavior mediated the relationship between treatment and STI hazard. A universal intervention for urban elementary school children, focused on classroom management and instruction, children's social competence, and parenting practices may reduce the onset of STI through age 30, especially for African Americans.

Temporal Sequencing Of Nicotine Dependence and Bipolar Disorder In The National Epidemiologic Survey On Alcohol and Related Conditions (NESARC). Martinez-Ortega JM, Goldstein BI, Gutierrez-Rojas L, Sala R, Wang S, Blanco C. J Psychiatr Res. 2013; 47(7): 858-864. Bipolar disorder (BD) and nicotine dependence (ND) often co-occur. However, the mechanisms underlying this association remain unclear. The authors aimed to examine, for the first time in a national and representative sample, the magnitude and direction of the temporal relationship between BD and ND; and to compare, among individuals with lifetime ND and BD, the sociodemographic and clinical characteristics of individuals whose onset of ND preceded the onset of BD (ND-prior) with those whose onset of ND followed the onset of BD (BD-prior). The sample included individuals with lifetime BD type I or ND (n=7,958) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43,093). Survival analyses and logistic regression models were computed to study the temporal association between ND and BD, and to compare ND-prior (n=135) and BD-prior (n=386) individuals. The authors found that ND predicted the onset of BD and BD also predicted the onset of ND. Furthermore, the risk of developing one disorder following the other one was greatest early in the course of illness. Most individuals with lifetime ND and BD were BD-

prior (72.6%). BD-prior individuals had an earlier onset of BD and a higher number of manic episodes. By contrast, ND-prior individuals had an earlier onset of both daily smoking and ND, and an increased prevalence of alcohol use disorder. In conclusion, ND and BD predict the development of each other. The phenomenology and course of ND and BD varied significantly depending on which disorder had earlier onset.

Characterizing Alcohol Use Disorders and Suicidal Ideation In Young Women. Agrawal A, Constantino AM, Bucholz KK, Glowinski A, Madden PAF, Heath AC, Lynskey MT. J Stud Alcohol Drugs. 2013; 74(3): 406-412.
Alcohol use disorders (AUDs) and suicidal ideation (SI) co-occur, yet few studies have investigated the risk and protective factors that influence their comorbidity. Data from 3,787 twin women ages 18-27 years were analyzed. AUD was defined as a lifetime history of alcohol abuse or dependence as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. SI was coded as a lifetime report of any SI, and all subjects were queried about SI. Subjects were divided into those with neither AUD nor SI (AUD-SI-), those with AUD but no SI (AUD+SI-), those with SI but no AUD (AUD-SI+), and those with comorbid AUD and SI (AUD+SI+). Association with multiple measures of psychopathology, negative life events, personality, and family history was assessed using multinomial logistic regression. Women with AUD were at 3.1 (95% confidence interval [2.5, 3.8]) odds of also reporting a lifetime history of SI. Psychopathology and negative life events were consistently high in the AUD+SI+ group. AUD+SI+ women also were more likely to report drinking to cope. Substance use was more common in the AUD+SI- versus the AUD-SI+ women, whereas major depressive disorder, social phobia, and panic attacks were more commonly reported by the AUD-SI+ versus the AUD+SI- women. The comorbidity between AUD and SI is characterized in young women by co-occurring psychopathology, drinking to cope, and negative life events.

Subtypes Of Disordered Gamblers: Results From the National Epidemiologic Survey On Alcohol and Related Conditions. Nower L, Martins SS, Lin K-H, Blanco C. Addiction. 2013; 108(4): 789-798.
The aim of this study was to derive empirical subtypes of problem gamblers based on etiological and clinical characteristics described in the Pathways Model, using data from a nationally representative survey of US adults. Data were collected from structured diagnostic face-to-face interviews using the Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV version IV (AUDADIS-IV). The study utilized data from US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). All disordered gambling participants (n = 581) from a nationally representative cross-sectional sample of civilian non-institutionalized adults aged 18 years or older. Latent class analyses indicated that the best-fitting model was a three-class solution. Those in the largest class (class 1: 50.76%, n = 295) reported the lowest overall levels of psychopathology including gambling problem severity and mood disorders. In contrast, respondents in class 2 (20.06%, n = 117) had a high probability of endorsing past-year substance use disorders, moderate probabilities of having parents with alcohol/drug problems and of having a personality disorder, and the highest probability for past-year mood disorders. Respondents in class 3 (29.18%, n = 169) had the highest probabilities of personality and prior-to-past year mood disorders, substance use disorders, separation/divorce, drinking-related physical fights and parents with alcohol/drug

problems and/or a history of antisocial personality disorder (ASPD).Three subtypes of disordered gamblers can be identified, roughly corresponding to the subtypes of the Pathways Model, ranging from a subgroup with low levels of gambling severity and psychopathology to one with high levels of gambling problem severity and comorbid psychiatric disorders.

Probability and Predictors Of Relapse To Smoking: Results Of the National Epidemiologic Survey On Alcohol and Related Conditions (NESARC). Garcia-Rodriguez O, Secades-Villa R, Florez-Salamanca L, Okuda M, Liu S-M, Blanco C. Drug Alcohol Depend. 2013.

The goal of this study was to estimate rates of relapse to smoking in the community and to identify predictors of relapse. Data were drawn from the Waves 1 and 2 of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Logistic regression analyses were used to estimate the probability of relapse at Wave 2 among individuals who were abstinent at Wave 1 given length of abstinence as well as the presence of several sociodemographic, psychopathologic and substance use-related variables at Wave 1. The risk for relapse among individuals who had been abstinent for 12 months or less at the baseline assessment was above 50%. Among individuals who had been abstinent for over a year, risk of relapse decreased hyperbolically as a function of time, and stabilized around 10% after 30 years of abstinence. Although several sociodemographic, psychopathologic and tobacco-related variables predicted relapse in univariate analyses, only younger age at cessation and shorter duration of abstinence independently predicted risk of relapse in multivariable analyses. The authors conclude that the first year after a quit attempt constitutes the period of highest risk for relapse. Although the risk for relapse decreases over time, it never fully disappears. Furthermore, younger age at smoking cessation also increases the risk for relapse. This information may help develop more targeted and effective relapse prevention programs.

Portfolios Of Biomedical HIV Interventions In South Africa: A Cost-Effectiveness Analysis. Long EF, Stavert, RR. J Gen Intern Med. 2013.

Recent clinical trials of male circumcision, oral pre-exposure prophylaxis (PrEP), and a vaginal microbicide gel have shown partial effectiveness at reducing HIV transmission, stimulating interest in implementing portfolios of biomedical prevention programs. The objective of this study was to evaluate the effectiveness and cost-effectiveness of combination biomedical HIV prevention and treatment scale-up in South Africa, given uncertainty in program effectiveness. The study design was a dynamic HIV transmission and disease progression model with Monte Carlo simulation and cost-effectiveness analysis. Participants were men and women aged 15 to 49 years in South Africa. Interventions included HIV screening and counseling, antiretroviral therapy (ART), male circumcision, PrEP, microbicide, and select combinations. Main measures obtained were HIV incidence, prevalence, discounted costs, discounted quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios. Results indicated that providing half of all uninfected persons with PrEP averts 28% of future HIV infections for $9,000/QALY gained, but the affordability of such a program is questionable. Given limited resources, annual HIV screening and ART utilization by 75% of eligible infected persons could avert one-third of new HIV infections, for approximately $1,000/QALY gained. Male circumcision is more cost-effective, but disproportionately benefits men. A comprehensive portfolio of expanded screening, ART, male circumcision, microbicides, and PrEP could avert 62% of new HIV infections, reducing HIV prevalence

from a projected 14% to 10% after 10 years. This strategy doubles treatment initiation and adds 31 million QALYs to the population. Despite uncertainty in program effectiveness, a comprehensive portfolio costs less than $10,000/QALY gained in 33% of simulation iterations and less than $30,000/QALY gained in 90% of iterations, assuming an annual microbicide cost of $100. The authors concluded that a portfolio of modestly-effective biomedical HIV prevention programs, including male circumcision, vaginal microbicides, and oral PrEP, could substantially reduce HIV incidence and prevalence in South Africa and be likely cost-effective. Given limited resources, PrEP is the least cost-effective intervention of those considered.

The Longitudinal Association Between Homelessness, Injection Drug Use, and Injection-Related Risk Behavior Among Persons With A History Of Injection Drug Use In Baltimore, MD. Linton SL, Celentano DD, Kirk GD, Mehta SH. Drug Alcohol Depend. 2013.

Few studies have assessed the temporal association between homelessness and injection drug use, and injection-related risk behavior. Among a cohort of 1,405 current and former injection drug users in follow-up from 2005 to 2009, the authors used random intercept models to assess the temporal association between homelessness and subsequent injection drug use, and to determine whether the association between homelessness and sustained injection drug use among active injectors differed from the association between homelessness and relapse among those who stopped injecting. The authors also assessed the association between homelessness and subsequent injection-related risk behavior among participants who injected drugs consecutively across two visits. Homelessness was categorized by duration: none, <1 month, and ≥1 month. Homelessness was reported on at least one occasion by 532 (38%) participants. The relationship between homelessness and subsequent injection drug use was different for active injectors and those who stopped injecting. Among those who stopped injecting, homelessness was associated with relapse [<1 month: AOR=1.67, 95% CI (1.01, 2.74); ≥1 month: AOR=1.34 95% CI (0.77, 2.33)]. Among active injectors, homelessness was not associated with sustained injection drug use [<1 month: AOR=1.03, 95% CI (0.71, 1.49); ≥1 month: AOR=0.81 95% CI (0.56, 1.17)]. Among those injecting drugs across two consecutive visits, homelessness ≥1 month was associated with subsequent injection-related risk behavior [AOR=1.61, 95% CI (1.06, 2.45)].The authors conclude that homelessness appears to be associated with relapse and injection-related risk behavior. Strengthening policies and interventions that prevent homelessness may reduce injection drug use and injection-related risk behaviors.

Anxiety Disorders and Drug Dependence: Evidence On Sequence and Specificity Among Adults. Goodwin RD, Stein DJ. Psychiatry Clin Neurosci. 2013; 67(3): 167-173.

The goal of this study was to investigate the relation between specific anxiety disorders and substance dependence, adjusting for potentially confounding demographic factors (e.g. sex) and comorbidity (e.g. alcohol dependence, major depression), among adults in the USA. Data were drawn from the National Comorbidity Survey (NCS), a nationally representative population sample of the US adult population aged 15-54. The temporal sequence of onset of anxiety and substance dependence disorders was examined. Substance dependence temporally precedes several anxiety disorders, particularly panic disorder. Specifically, a history of past substance dependence predicts current panic disorder (odds ratio [OR]=2.62, 95% confidence

interval [CI]=1.29, 5.32), social phobia (OR=1.7, 95%CI=1.12, 2.41), and agoraphobia (OR=1.78, 95%CI=1.08, 2.94). Conversely, in more than 50% of substance abuse disorder cases, in nearly 40% of post-traumatic stress disorder (PTSD) cases, and in nearly 30% of generalized anxiety disorder (GAD) cases, the anxiety disorder has first onset. Similarly, a lifetime history of social phobia, PTSD, or GAD significantly predicts lifetime substance dependence (OR=1.51 for social phobia, 2.06 for PTSD, 1.45 for GAD). For any particular anxiety disorder, a diagnosis of substance abuse can occur prior to or subsequent to an anxiety disorder. Nevertheless, there is also evidence for the specificity of some associations between anxiety and substance dependence disorders; these are independent of the effects of sex and other comorbid disorders, may be causal in nature, and deserve particular attention in clinical settings. The possibility that within a particular anxiety disorder there are a variety of mechanisms of association with various substances should be addressed in future work.

"Eyes That Don't See, Heart That Doesn't Feel": Coping With Sex Work In Intimate Relationships and Its Implications For HIV/STI Prevention. Syvertsen JL, Robertson AM, Rolon ML, Palinkas LA, Martinez G, Rangel M, Gudelia SS. Soc Sci Med. 2013; 87: 1-8.
Partner communication about HIV sexual risk behaviors represents a key area of epidemiologic and social importance in terms of infection acquisition and potential for tailored interventions. Nevertheless, disclosing sexual risk behaviors often presents myriad challenges for marginalized couples who engage in stigmatized behaviors. Using qualitative data from a social epidemiology study of risk for HIV and other sexually transmitted infections (STIs) among female sex workers and their intimate, non-commercial male partners along the Mexico-U.S. border, the authors examined both partners' perspectives on sex work and the ways in which couples discussed associated HIV/STI risks in their relationship. Their thematic analysis of individual and joint interviews conducted in 2010 and 2011 with 44 couples suggested that broader contexts of social and economic inequalities profoundly shaped partner perspectives of sex work. Although couples accepted sex work as an economic contribution to the relationship in light of limited alternatives and drug addiction, it exacted an emotional toll on both partners. Couples employed multiple strategies to cope with sex work, including psychologically disconnecting from their situation, telling "little lies," avoiding the topic, and to a lesser extent, superficially discussing their risks. While such strategies served to protect both partners' emotional health by upholding illusions of fidelity and avoiding potential conflict, non-disclosure of risk behaviors may exacerbate the potential for HIV/STI acquisition. This work has direct implications for designing multi-level, couple-based health interventions.

Measurement Invariance Of DSM-IV Alcohol, Marijuana and Cocaine Dependence Between Community-Sampled and Clinically Overselected Studies. Derringer J, Krueger RF, Dick DM, Agrawal A, Bucholz KK, Foroud T, Grucza RA, Hesselbrock MN, Hesselbrock V, Kramer J, Nurnberger Jr. JI, Schuckit M, Bierut LJ, Iacono WG, McGue M. Addiction. 2013.
The aims of this study were to examine whether DSM-IV symptoms of substance dependence are psychometrically equivalent between existing community-sampled and clinically over selected studies. Participants were a total of 2,476 adult twins born in Minnesota and 4,121 unrelated adult participants from a case-control study of alcohol dependence. Measurements obtained were life-time DSM-IV alcohol, marijuana and cocaine dependence symptoms and

ever use of each substance. The authors fitted a hierarchical model to the data, in which ever use and dependence symptoms for each substance were indicators of alcohol, marijuana or cocaine dependence which were, in turn, indicators of a multi-substance dependence factor. The authors then tested the model for measurement invariance across participant groups, defined by study source and participant sex. The hierarchical model fitted well among males and females within each sample [comparative fit index (CFI) > 0.96, Tucker-Lewis index (TLI) > 0.95 and root mean square error of approximation (RMSEA) < 0.04 for all], and a multi-group model demonstrated that model parameters were equivalent across sample- and sex-defined groups (ΔCFI = 0.002 between constrained and unconstrained models). Differences between groups in symptom endorsement rates could be expressed solely as mean differences in the multi-substance dependence factor. The authors conclude that life-time substance dependence symptoms fitted a dimensional model well. Although clinically over selected participants endorsed more dependence symptoms, on average, than community-sampled participants, the pattern of symptom endorsement was similar across groups. From a measurement perspective, DSM-IV criteria are equally appropriate for describing substance dependence across different sampling methods.

The Association Between Law Enforcement Encounters and Syringe Sharing Among IDUs on Skid Row: A Mixed Methods Analysis. Wagner KD, Simon-Freeman R, Bluthenthal RN. AIDS Behav. 2013.

The legal environment is one factor that influences injection drug users' (IDUs) risk for HIV and other blood borne pathogens such as hepatitis C virus (HCV). The authors examined the association between law enforcement encounters (i.e., arrests and citations) and receptive syringe sharing among IDUs in the context of an intensified policing effort. They conducted a mixed methods analysis of 30 qualitative and 187 quantitative interviews with IDUs accessing services at a Los Angeles, CA syringe exchange program from 2008 to 2009. Qualitative findings illustrate concerns related to visibility, drug withdrawal, and previous history of arrest/incarceration. In quantitative analysis, the number of citations received, current homelessness, and perceiving that being arrested would be a "big problem" were independently associated with recent syringe sharing. Findings illustrate some of the unintended public health consequences associated with intensified street-level policing, including risk for HIV and HCV transmission.

Patterns Of Injection Drug Use Cessation During An Expansion Of Syringe Exchange Services In A Canadian Setting. Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood E. Drug Alcohol Depend. 2013.

Needle and syringe programmes (NSPs) have been shown to reduce HIV risk among people who inject drugs (IDUs). However, concerns remain that NSPs delay injecting cessation. Individuals reporting injection drug use in the past six months in the greater Vancouver area were enrolled in the Vancouver Injection Drug Users Study (VIDUS). Annual estimates of the proportion of IDU reporting injecting cessation were generated. Generalized estimating equation (GEE) analysis was used to assess factors associated with injecting cessation during a period of NSP expansion. Between May 1996 and December 2010, the number of NSP sites in Vancouver increased from 1 to 29 (P<0.001). The estimated proportion of participants (n=2710) reporting cessation increased from 2.4% (95% confidence interval [CI]: 0.0-7.0%) in 1996 to 47.9% (95% CI: 46.8-48.9%) in 2010 (P<0.001). In a multivariate GEE analysis, the

authors observed an association between increasing calendar year and increased likelihood of injecting cessation (Adjusted Odds Ratio=1.17, 95% CI: 1.15, 1.19, P<0.001). The authors conclude that the proportion of IDU reporting injecting cessation increased during a period of NSP expansion, implying that increased NSP availability did not delay injection cessation. These results should help inform community decisions on whether to implement NSPs.

Using Peer Ethnography To Address Health Disparities Among Young Urban Black and Latino Men Who Have Sex With Men. Mutchler MG, McKay T, McDavitt B, Gordon KK. Am J Public Health. 2013; 103(5): 849-852.
The authors examined the effectiveness of peer ethnography to gain insider views on substance use and sex among a diverse range of high-risk substance-using Black and Latino young men who have sex with men. They recruited 9 peer ethnographers aged 21 to 24 years from youth programs for the lesbian, gay, bisexual, and transgender community in Los Angeles, California, and trained them in ethnography, study protocol, and human participant protection. Peer ethnographers collected 137 single-spaced pages of field notes in 2009 and 2010 derived from observation of 150 members of the target population. Peer ethnography revealed local language and phrasing and provided a window into new and different social contexts. Peers provided valuable information on current trends in substance use, revealing themes that needed to be addressed in further research, such as the use of substances during sex to "clock coin" (exchange sex for money and substances). These data enabled the authors to refine their recruitment strategies and ask more culturally relevant questions in a later phase of the study.The peer ethnography method can provide a sound basis for further research phases in multistage studies on numerous other social issues and with other hard-to-reach populations.

Adolescents' Access to Their Own Prescription Medications in the Home. Ross-Durow PL, McCabe SE, Boyd CJ. J Adolesc Health. 2013.
The objective of this descriptive study was to determine adolescents' access to their own medications at home, specifically prescription pain, stimulant, antianxiety, and sedative medications. Semistructured interviews were conducted with a cohort of 501 adolescents from two southeastern Michigan school districts. Participants were asked what medications had been prescribed to them during the previous 6 months; if they had received prescription medications, they were asked in-depth questions about them, including how medications were stored and supervised at home. The sample was comprised of adolescents in the 8th and 9th grades, and 50.9% were male. Participants were primarily white (72.9%, n= 365) or African-American (21.6%, n= 108). Slightly less than half of the adolescents (45.9%, n= 230) reported having been prescribed medications in the previous 6 months. Of this group, 14.3% (n= 33) had been prescribed pain medications, 9.6% (n= 22) stimulants, 1.7% (n= 4) antianxiety medications, and .9% (n= 2) sedatives. In total, 57 adolescents were prescribed medications in the pain, stimulant, antianxiety, or sedative categories (including controlled medications), and the majority (73.7%, n= 42) reported that they had unsupervised access to medications with abuse potential. The majority of adolescents who were prescribed medications in the pain, stimulant, antianxiety, or sedative categories during the previous 6 months had unsupervised access to them at home. It is critical that clinicians educate parents and patients about the importance of proper storage and disposal of medications, particularly those with abuse potential.

Mental Illness and Lost Income Among Adult South Africans. Lund C, Myer L, Stein DJ, Williams DR, Flisher AJ. Soc Psychiatry Psychiatr Epidemiol. 2013; 48(5): 845-851.
Little is known regarding the links between mental disorder and lost income in low- and middle-income countries. The purpose of this study was to investigate the association between mental disorder and lost income in the first nationally representative psychiatric epidemiology survey in South Africa. A probability sample of South African adults was administered the World Health Organization Composite International Diagnostic Interview schedule to assess the presence of mental disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, version IV. The presence of severe depression or anxiety disorders was associated with a significant reduction in earnings in the previous 12 months among both employed and unemployed South African adults ($p = 0.0043$). In simulations of costs to individuals, the mean estimated lost income associated with severe depression and anxiety disorders was $4,798 per adult per year, after adjustment for age, gender, substance abuse, education, marital status, and household size. Projections of total annual cost to South Africans living with these disorders in lost earnings, extrapolated from the sample, were $3.6 billion. These data indicate either that mental illness has a major economic impact, through the effect of disability and stigma on earnings, or that people in lower income groups are at increased risk of mental illness. The indirect costs of severe depression and anxiety disorders stand in stark contrast with the direct costs of treatment in South Africa, as illustrated by annual government spending on mental health services, amounting to an estimated $59 million for adults. The findings of this study support the economic argument for investing in mental health care as a means of mitigating indirect costs of mental illness.

Social-Information-Processing Patterns Mediate the Impact Of Preventive Intervention On Adolescent Antisocial Behavior. Dodge KA, Godwin J. Psychol Sci. 2013; 24(4): 456-465.
In the study reported here, the authors tested the hypothesis that the Fast Track preventive intervention's positive impact on antisocial behavior in adolescence is mediated by its impact on social-cognitive processes during elementary school. Fast Track is the largest and longest federally funded preventive intervention trial for children showing aggressive behavior at an early age. Participants were 891 high-risk kindergarten children (69% male, 31% female; 49% ethnic minority, 51% ethnic majority) who were randomly assigned to an intervention or a control group by school cluster. Multiyear intervention addressed social-cognitive processes through social-skill training groups, parent groups, classroom curricula, peer coaching, and tutoring. Assigning children to the intervention decreased their mean antisocial-behavior score after Grade 9 by 0.16 standardized units ($p < .01$). Structural equation models indicated that 27% of the intervention's impact on antisocial behavior was mediated by its impact on three social-cognitive processes: reducing hostile-attribution biases, increasing competent response generation to social problems, and devaluing aggression. These findings support a model of antisocial behavioral development mediated by social-cognitive processes, and they guide prevention planners to focus on these processes.

Toward Rigorous Idiographic Research In Prevention Science: Comparison Between Three Analytic Strategies For Testing Preventive Intervention In Very Small Samples. Ridenour TA, Pineo TZ, Maldonado Molina MM, Hassmiller Lich K. Prev Sci. 2013; 14(3): 267-278.

Psychosocial prevention research lacks evidence from intensive within-person lines of research to understand idiographic processes related to development and response to intervention. Such data could be used to fill gaps in the literature and expand the study design options for prevention researchers, including lower-cost yet rigorous studies (e.g., for program evaluations), pilot studies, designs to test programs for low prevalence outcomes, selective/indicated/adaptive intervention research, and understanding of differential response to programs. This study compared three competing analytic strategies designed for this type of research: autoregressive moving average, mixed model trajectory analysis, and P-technique. Illustrative time series data were from a pilot study of an intervention for nursing home residents with diabetes (N=4) designed to improve control of blood glucose. A within-person, intermittent baseline design was used. Intervention effects were detected using each strategy for the aggregated sample and for individual patients. The P-technique model most closely replicated observed glucose levels. ARIMA and P-technique models were most similar in terms of estimated intervention effects and modeled glucose levels. However, ARIMA and P-technique also were more sensitive to missing data, outliers and number of observations. Statistical testing suggested that results generalize both to other persons as well as to idiographic, longitudinal processes. This study demonstrated the potential contributions of idiographic research in prevention science as well as the need for simulation studies to delineate the research circumstances when each analytic approach is optimal for deriving the correct parameter estimates.

Protective Parenting, Relationship Power Equity, and Condom Use Among Rural African American Emerging Adult Women. Kogan SM, Simons LG, Chen Y, Burwell S, Brody GH. Fam Relat. 2013; 62(2): 341-353.

Sexually transmitted infections disproportionately affect African Americans, particularly young women. The influence of a set of interrelated protective parenting processes-instrumental and emotional support, sexual risk communication, and encouragement of goals for employment or education-on emerging adult women was examined. Parenting was hypothesized to affect consistent condom use through its association with women's reports of power equity in their intimate relationships. Hypotheses were tested with 135 sexually active women 18 to 21 years of age living in rural southern communities. Structural equation modeling indicated that (a) parenting processes predicted women's self-reported relationship power equity and consistent condom use, and (b) relationship power equity predicted consistent condom use. Limited support emerged for a mediational role of relationship power equity in explaining the influence of parenting on consistent condom use. Parental involvement and young women's establishment of personal control in their intimate relationships are important goals for sexual risk reduction programs.

Trends In the Prevalence Of Tobacco Use In the United States, 1991-1992 to 2004-2005. Secades-Villa R, Olfson M, Okuda M, Velasquez N, Perez-Fuentes G, Liu S-M, Blanco C. Psychiatr Serv. 2013; 64(5): 458-465.
This study examined changes in the prevalence of daily tobacco use in the United States between 1991-1992 and 2004-2005 by sociodemographic characteristics and psychiatric disorders. Secondary analyses were performed using data from the National Longitudinal Alcohol Epidemiologic Survey, conducted in 1991-1992 (N=41,612), and wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions, conducted in 2004-2005 (N=34,653). Although the overall prevalence of past-year daily tobacco use decreased significantly, the reduction was not uniform across all segments of the population. In both surveys, past-year daily tobacco use was higher among respondents with a drug use disorder, an alcohol use disorder, and major depressive disorder and among individuals from socioeconomically disadvantaged groups. Declines in use were slower among individuals with a lifetime alcohol use disorder or major depressive disorder. The prevalence of past-year daily tobacco use did not decrease among Native Americans. The authors conclude that individuals with substance use disorders or major depressive disorder and Native Americans reported higher rates of past-year daily tobacco use than the general population. These findings suggest the need to emphasize specific interventions for these groups.

School Mental Health Resources and Adolescent Mental Health Service Use. Green JG, McLaughlin KA, Alegria M, Costello EJ, Gruber MJ, Hoagwood K, Leaf PJ, Olin S, Sampson NA, Kessler RC. J Am Acad Child Adolesc Psychiatry. 2013; 52(5): 501-510.
Although schools are identified as critical for detecting youth mental disorders, little is known about whether the number of mental health providers and types of resources that they offer influence student mental health service use. Such information could inform the development and allocation of appropriate school-based resources to increase service use. This article examines associations of school resources with past-year mental health service use among students with 12-month DSM-IV mental disorders. Data come from the U.S. National Comorbidity Survey Adolescent Supplement (NCS-A), a national survey of adolescent mental health that included 4,445 adolescent-parent pairs in 227 schools in which principals and mental health coordinators completed surveys about school resources and policies for addressing student emotional problems. Adolescents and parents completed the Composite International Diagnostic Interview and reported mental health service use across multiple sectors. Multilevel multivariate regression was used to examine associations of school mental health resources and individual-level service use. Nearly half (45.3%) of adolescents with a 12-month DSM-IV disorder received past-year mental health services. Substantial variation existed in school resources. Increased school engagement in early identification was significantly associated with mental health service use for adolescents with mild/moderate mental and behavior disorders. The ratio of students to mental health providers was not associated with overall service use, but was associated with sector of service use. School mental health resources, particularly those related to early identification may facilitate mental health service use and may influence sector of service use for youths with DSM disorders.

Individual, Interpersonal, and Social-Structural Correlates Of Involuntary Sex Work Among Female Sex Workers In Two Mexico-U.S. Border Cities. Goldenberg SM, Rangel G, Staines H, Vera A, Lozada R, Nguyen L, Silverman JG, Strathdee SA. Individual, Interpersonal, And Social-Structural Correlates Of Involuntary Sex Work Among Female Sex Workers In Two Mexico-U.S. Border Cities. J Acquir Immune Defic Syndr. 2013.
The objective of the present study was to investigate individual, interpersonal, and social-structural factors associated with involuntary sex work among female sex workers (FSWs) along the Mexico-U.S. border. In 2010-2011, 214 FSWs from Tijuana (n=106) and Ciudad Juarez (n=108) aged 18 years who reported lifetime use of heroin, cocaine, crack, or methamphetamine, having a stable partner, and having sold/traded sex in the past month completed quantitative surveys and HIV/STI testing. Logistic regression was used to identify correlates of involuntary sex work among FSWs. Of 214 FSWs, 31 (14.5%) reported involuntary sex work. These women were younger at sex work entry (Adjusted odds ratio [AOR]: 0.84/1 year increase, 95% CI: 0.72-0.97) and were significantly more likely to service clients whom they perceived to be HIV/STI-infected (AOR: 12.41, 95% CI: 3.15-48.91). Additionally, they were more likely to have clients who used drugs (AOR: 7.88, 95% CI: 1.52-41.00), report poor working conditions (AOR: 3.27, 95% CI: 1.03-10.31), and report a history of rape (AOR: 4.46, 1.43-13.91). The authors conclude that involuntary sex work is disproportionate among FSWs who initiate sex work at a younger age, and these women experience elevated risk of violence and HIV/STIs related to their clients' behaviors and their working conditions. These data suggest the critical need for evidence-based approaches to preventing sexual exploitation of women and girls and to reducing harm among current sex workers. Multi-level interventions for sex workers and their clients that target interpersonal and social-structural risks (e.g., measures to improve safety and reduce exploitation within the workplace) are needed.

Effects Of Independent and Substance-Induced Major Depressive Disorder On Remission and Relapse Of Alcohol, Cocaine and Heroin Dependence. Samet S, Fenton MC, Nunes E, Greenstein E, Aharonovich E, Hasin D.\ Addiction. 2013; 108(1): 115-123.
Little is known about the differential effects of independent and substance-induced major depression on the longitudinal course of alcohol, cocaine and heroin disorders when studied prospectively. Consecutively admitted in-patients, were evaluated at baseline, 6-, 12- and 18-month follow-ups. Baseline evaluations were conducted in a short-stay in-patient urban community psychiatric hospital unit. Adults (n = 250) with current DSM-IV cocaine, heroin and/or alcohol dependence at baseline served as participants. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM), was used to evaluate independent and substance-induced major depression, alcohol, cocaine and heroin dependence, and other psychiatric disorders. Outcomes for each substance: (i) time (weeks) from hospital discharge to first use; (ii) time from discharge to onset of sustained (≥26 weeks) remission from dependence; (iii) time from onset of sustained remission to relapse. Substance-induced major depression significantly predicted post-discharge use of alcohol, cocaine and heroin (hazard ratios 4.7, 5.3 and 6.5, respectively). Among patients achieving stable remissions from dependence, independent major depression predicted relapse to alcohol and cocaine dependence (hazard ratios 2.3 and 2.7, respectively). Substance-induced and independent major depressions were both related to post-discharge use of alcohol, cocaine and heroin. The

findings suggest the importance of clinical attention to both types of depression in substance abusing patients.

Volatile Substance Misuse: Toward A Research Agenda. Howard MO, Garland EL. Am J Drug Alcohol Abuse. 2013; 39(1): 3-7.
Volatile substance misuse (VSM) is a significant but under-researched global health problem. This perspective calls for additional VSM research in key areas including the phenomenology and adverse health and social consequences of acute inhalant intoxication and for prospective longitudinal studies of the natural history of VSM and related deleterious long-term biomedical and psychosocial outcomes. Taxonomic investigations are needed to identify subtypes of volatile substance misusers (VSMs), whereas qualitative and mixed methods evaluations would provide important information about cultural and interpersonal contexts and specific patterns, modalities and agents of VSM. Treatment outcome and health services studies have rarely been conducted with reference to VSMs and are needed. Studies of specific inhalants and high-risk populations for VSM would also contribute to current knowledge regarding VSM and help reduce the toll taken by this prevalent form of drug misuse. The authors draw on VSM studies that they and other researchers have conducted to exemplify the types of research needed in each of the domains identified above. Despite the global ubiquity of VSM, much remains to be learned about this form of substance use. This perspective identifies key elements of a systematic program for research in this area.

Smoking Status, Physical Health-Related Quality Of Life, and Mortality In Middle-Aged and Older Women. Holahan CK, Holahan CJ, North RJ, Hayes RB, Powers DA, Ockene JK. Nicotine Tob Res. 2013; 15(3): 662-669.
Women who smoke, particularly older women, have been relatively neglected in smoking research. There is a lack of knowledge concerning the relation of level of smoking to quality of life and mortality among middle-aged and older women smokers. This study examined the relation of smoking status to physical health-related quality of life (PHRQL) and total mortality in women in the Women' Health Initiative (WHI) Observational Study. Participants were 90,849 postmenopausal women, who were an average age of 63.6 years at baseline. Analyses used multiple linear and Cox proportional hazards regression and controlled for age, educational level, and ethnicity. Never-smokers were the reference group. The authors found that smoking status was significantly related to PHRQL cross-sectionally at baseline and prospectively at a 3-year follow-up, with those who smoked having lower PHRQL. Heavier smokers showed large, clinically meaningful associations with PHRQL and light smokers showed small associations. In addition, they found that the smoking status at baseline was significantly related to 10-year total mortality. Both light and heavier smoking at baseline significantly correlated with higher mortality risk; however, the relationship of smoking to mortality was dose dependent. Among former smokers, those who had smoked longer showed significantly lower PHRQL and significantly increased mortality risk. Findings suggest that the risks of smoking may not be evident to light smokers and that educational interventions targeted to middle-aged and older women stressing the consequences of light smoking may be particularly beneficial.

Alcohol Problems As A Signal For Sensitivity To Nicotine Dependence and Future Smoking. Dierker L, Selya A, Piasecki T, Rose J, Mermelstein R. Drug Alcohol Depend. 2013.

Alcohol use is a well-documented risk factor for the emergence of chronic smoking behavior. Very little is known, however, about the mediating pathways through which alcohol and/or alcohol-related problems influence future smoking. Data were drawn from the longitudinal Social and Emotional Contexts of Adolescent Smoking Patterns Study (SECASPS). Adolescents who had smoked under 100 cigarettes in their lifetime (n=898; experimenters) and adolescents who had smoked over 100 cigarettes, but fewer than 5 cigarettes per day (n=152: current smokers) were examined separately (grouping variable). Path analysis was performed to investigate the association between alcohol related problems at baseline (primary predictor) and smoking regularity at the 48month follow-up (primary outcome), both directly and through mediating variables of smoking quantity and frequency, and nicotine dependence (averaged across these measures at 6-, 15-, and 24-month assessment waves). Among experimenters, after controlling for smoking and alcohol use, the association between alcohol-related problems at baseline and smoking frequency 48months later was fully mediated by nicotine dependence symptoms. Among current smokers, only past smoking behavior was associated with 48-month smoking frequency. The authors conclude that alcohol-related problems are a risk factor for future smoking among novice adolescent smokers above and beyond drinking or smoking per se. By signaling sensitivity to nicotine dependence symptoms, alcohol related problems represent an easily measureable risk factor that can be used to identify and intervene with adolescents before more chronic smoking behaviors emerge.

Combined Role Of Childhood Maltreatment, Family History, and Gender In the Risk For Alcohol Dependence. Fenton MC, Geier T, Keyes K, Skodol AE, Grant BF, Hasin DS. Psychol Med. 2013; 43(5): 1045-1057.

Studies of the relationship between childhood maltreatment and alcohol dependence have not controlled comprehensively for potential confounding by co-occurring maltreatments and other childhood trauma, or determined whether parental history of alcohol disorders operates synergistically with gender and maltreatment to produce alcohol dependence. The authors addressed these issues using national data. The method employed were face-to-face surveys of 27,712 adult participants in a national survey. Childhood physical, emotional and sexual abuse, and physical neglect were associated with alcohol dependence ($p<0.001$), controlling for demographics, co-occurring maltreatments and other childhood trauma. Attributable proportions (APs) due to interaction between each maltreatment and parental history revealed significant synergistic relationships for physical abuse in the entire sample, and for sexual abuse and emotional neglect in women (APs, 0.21, 0.31, 0.26 respectively), indicating that the odds of alcohol dependence given both parental history and these maltreatments were significantly higher than the additive effect of each alone ($p<0.05$). Childhood maltreatments independently increased the risk of alcohol dependence. Importantly, results suggest a synergistic role of parental alcoholism: the effect of physical abuse on alcohol dependence may depend on parental history, while the effects of sexual abuse and emotional neglect may depend on parental history among women. Findings underscore the importance of early identification and prevention, particularly among those with a family history, and could guide genetic research and intervention development, e.g. programs to reduce the burden of childhood maltreatment may benefit from addressing the negative long-term effects of

maltreatments, including potential alcohol problems, across a broad range of childhood environments.

Drug Use Patterns In Young Adulthood and Post-College Employment. Arria AM, Garnier-Dykstra LM, Cook ET, Caldeira KM, Vincent KB, Baron RA, O'Grady KE. Drug Alcohol Depend. 2013; 127(1-3): 23-30.
The relationship between serious drug involvement and risk for unemployment is well recognized, but few studies have prospectively examined this relationship among college students. This study used longitudinal data to examine the association between drug use patterns during college and the likelihood of employment post-college, holding constant sociodemographic variables and personality characteristics. Second, the authors estimate the prevalence of alcohol and other drug use disorders among employed individuals. Data were derived from the College Life Study. Participants entered college as traditional students and were assessed annually for six years, regardless of continued college attendance. Analyses were restricted to 620 individuals no longer enrolled in school by Year 6. Using multinomial regression modeling, persistent drug users (i.e., used illicit drugs (other than marijuana) and/or nonmedical prescription drugs every year they were assessed during the first four years of study) were significantly more likely than non-users to be unemployed vs. employed full-time post-college. Persistent drug users and infrequent marijuana users were also more likely than non-users to be unemployed vs. employed part-time. In Year 6, 13.2% of individuals employed full-time and 23.7% of individuals employed part-time met DSM-IV criteria for drug abuse or dependence during the past year. If confirmed, the results of this study suggest that persistent drug use among academically achieving young adults might increase risk for post-college unemployment. More research is needed to understand the processes underlying this association. Further attention should be directed at managing substance use problems among recent college graduates who have secured employment.

Acculturation and Drug Use Disorders Among Hispanics In the U.S. Blanco C, Morcillo C, Alegria M, Dedios MC, Fernandez-Navarro P, Regincos R, Wang S. J Psychiatr Res. 2013; 47(2): 226-232.
The authors' objective was to examine the relationship between degree of acculturation across five different dimensions of acculturation and risk of drug use disorders (DUD) among US Hispanics. Data were derived from a large national sample of the US adult population, the National Epidemiological Survey on Alcohol and Related Conditions, collected using face-to-face interviews. The sample included civilian non-institutionalized U.S. population aged 18 years and older, with oversampling of Hispanics, Blacks and those aged 18-24 years. Interviews of more than 34,000 adults were conducted during 2004-2005 using the Alcohol Use Disorder and Associated Disabilities Interview Schedule - DSM-IV Version. A total of 6,359 subjects who identified themselves as Hispanics were included in this study. Acculturation measures used in this study assessed, time spent in the U.S., age at immigration, language preference, social network composition, and ethnic identification. Among Hispanics, there was an inverse relationship between five complementary dimensions of acculturation and DUD. Moreover, this relationship showed a significant gradient across all acculturation dimensions and DUD. The prevalence of DUD increases with acculturation in Hispanics, across several measures of acculturation in a dose-response relationship. Hispanic cultural

features and values exert a protective effect on risk of DUD. Preservation and promotion of Hispanic values may be an important component of preventive interventions for Hispanics.

Dispelling the Myth Of "Smart Drugs": Cannabis and Alcohol Use Problems Predict Nonmedical Use Of Prescription Stimulants For Studying. Arria AM, Wilcox HC, Caldeira KM, Vincent KB, Garnier-Dykstra LM, O'Grady KE. Addict Behav. 2013; 38(3):1643-1650. This study tested the hypothesis that college students' substance use problems would predict increases in skipping classes and declining academic performance, and that nonmedical use of prescription stimulants (NPS) for studying would occur in association with this decline. A cohort of 984 students in the College Life Study at a large public university in the US participated in a longitudinal prospective study. Interviewers assessed NPS; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) cannabis and alcohol use disorders; and frequency of skipping class. Semester grade point average (GPA) was obtained from the university. Control variables were race, sex, family income, high school GPA, and self-reported attention deficit hyperactivity disorder diagnosis. Longitudinal growth curve modeling of four annual data waves estimated the associations among the rates of change of cannabis use disorder, percentage of classes skipped, and semester GPA. The associations between these trajectories and NPS for studying were then evaluated. A second structural model substituted alcohol use disorder for cannabis use disorder. More than one-third (38%) reported NPS for studying at least once by Year 4. Increases in skipping class were associated with both alcohol and cannabis use disorder, which were associated with declining GPA. The hypothesized relationships between these trajectories and NPS for studying were confirmed. These longitudinal findings suggest that escalation of substance use problems during college is related to increases in skipping class and to declining academic performance. NPS for studying is associated with academic difficulties. Although additional research is needed to investigate causal pathways, these results suggest that nonmedical users of prescription stimulants could benefit from a comprehensive drug and alcohol assessment to possibly mitigate future academic declines.

The Bidirectional Relationships Between Alcohol, Cannabis, Co-Occurring Alcohol and Cannabis Use Disorders With Major Depressive Disorder: Results From A National Sample. Pacek LR, Martins SS, Crum RM. J Affect Disord. 2013; 148(2-3): 188-195. Alcohol use disorders (AUD) and cannabis use disorders (CUD) are common in the United States (US), and are associated with major depressive disorder (MDD). Co-occurring alcohol and cannabis use/use disorders (AUD+CUD), though understudied, have been found to be associated with greater adverse outcomes than alcohol or cannabis use/use disorders alone. There is a paucity of research on the co-occurring relationships of the two disorders with depression. Data came from Waves 1 and 2 of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), a population-based longitudinal survey of the adult non-institutionalized, civilian population in the US. Logistic regression analyses were used to assess the associations between: 1) baseline AUD, CUD, and co-occurring AUD+CUD with incident MDD at follow-up and 2) baseline MDD with incident AUD, CUD, and co-occurring AUD+CUD at follow-up, adjusted for potential confounding variables. For Aim 1, most of the AUD and CUD were positively associated with MDD. The strongest associations with incident MDD were observed for cannabis dependence (OR=6.61, CI=1.67-26.21) and co-occurring alcohol and cannabis dependence (OR=2.34, CI=1.23-4.48). For Aim 2, baseline MDD was

significantly associated with comparatively fewer cases of incident AUD and CUD but the strongest association was observed for new onset co-occurring alcohol and cannabis dependence (OR=4.51, CI=1.31-15.60).The present study is limited by the potential for social desirability and recall biases. Positive associations between AUD, CUD and MDD were observed bidirectionally. Findings have implications for preventive and treatment programs and initiatives.

Leftover Prescription Opioids and Nonmedical Use Among High School Seniors: A Multi-Cohort National Study. McCabe SE, West BT, Boyd CJ. J Adolesc Health. 2013; 52(4): 480-485.

The aims of the present study were to (1) estimate the proportion of nonmedical users of prescription opioids (i.e., used prescription opioids in the past year without a doctor's orders) who used leftover medications from their own previous prescriptions; (2) assess substance use behaviors as a function of diversion source; and (3) identify the sources for these prescribed opioids. The authors analyzed data collected via self-administered questionnaires from nationally representative samples of high school seniors (modal age, 18 years) as a part of the Monitoring the Future (MTF) study. The sample consisted of four cohorts (senior years of 2007-2010, n= 8,888), including 647 high school seniors who reported past-year nonmedical use of prescription opioids, of whom 53% were estimated to be women. An estimated 36.9% of past-year nonmedical users of prescription opioids obtained these opioid medications from their own previous prescriptions. Logistic regression analyses indicated that nonmedical users who used leftover medications from their previous prescriptions were primarily motivated to relieve physical pain, whereas nonmedical users who obtained medications from other sources had significantly higher odds of prescription opioid abuse and other substance use behaviors. Based on a subanalysis of nonmedical users who obtained prescription opioids from their previous prescriptions in 2010 (n= 51), approximately 27.1% obtained them from a dentist, 45.0% obtained them from an emergency room physician, and 38.3% obtained them from another physician. Leftover prescription opioids from previous prescriptions represent a major source of nonmedical use of prescription opioids among high school seniors. These findings indicate that enhanced vigilance is needed when prescribing and monitoring prescription opioids among adolescents, to reduce leftover medications and nonmedical use.

Drug Use Patterns and Continuous Enrollment In College: Results From A Longitudinal Study. Arria AM, Garnier-Dykstra LM, Caldeira KM, Vincent KB, Winick ER, O'Grady KE. J Stud Alcohol Drugs. 2013; 74(1): 71-83.

Few longitudinal studies have examined the relationship between illicit drug use and academic outcomes among college students. This study characterized drug use patterns of a cohort of young adults who were originally enrolled as first-time, first-year college students in a longitudinal study. It evaluated the association between these drug use patterns and continuous enrollment during college, holding constant demographic characteristics, high school grade point average, fraternity/sorority involvement, personality/temperament characteristics, nicotine dependence, and alcohol use disorder. Participants (n = 1,133; 47% male) were purposively selected from one university and interviewed annually for 4 years, beginning with their first year of college, regardless of continued college attendance. Enrollment data were culled from administrative records. Group-based trajectory analyses characterized 4-year longitudinal drug use patterns. Two grouping variables were derived based on (a) marijuana

use frequency and (b) number of illicit drugs used other than marijuana. Seventy-one percent of the sample was continuously enrolled in the home institution during the first 4 years of study. Multivariable logistic regression models demonstrated that infrequent, increasing, and chronic/heavy marijuana use patterns were significantly associated with discontinuous enrollment (adjusted odds ratio = 1.66, 1.74, and 1.99, respectively), compared with minimal use, holding constant covariates. In separate models, drug use other than marijuana also was significantly associated with discontinuous enrollment. Marijuana use and other illicit drug use are both associated with a decreased likelihood of continuous enrollment in college, independent of several other possible risk factors. These findings highlight the need for early intervention with illicit drug users to mitigate possible negative academic consequences.

Medical Use, Medical Misuse, and Nonmedical Use Of Prescription Opioids: Results From A Longitudinal Study. McCabe SE, West BT, Boyd CJ. Pain. 2013; 154(5): 708-713.
The objective of this study was to examine the prevalence and patterns associated with past-year medical use, medical misuse, and nonmedical use of prescription opioids (NMUPO) among adolescents over a 2-year time period and to examine substance abuse, sleeping problems, and physical pain symptoms associated with these patterns of medical use, medical misuse, and NMUPO. A Web-based survey was self-administered by a longitudinal sample of 2050 middle and high school students in 2009-2010 (Year 1) and again in 2010-2011 (Year 2). The study was set in 2 southeastern Michigan school districts. The longitudinal sample consisted of 50% females, 67% Whites, 28% African-Americans, and 5% from other racial/ethnic categories. Main outcome measures were past-year medical use, medical misuse, and NMUPO. Of those reporting appropriate medical use of prescription opioids in Year 1, approximately 34% continued medical use in Year 2. Of those reporting past-year NMUPO in Year 1, approximately 25% continued NMUPO in Year 2. Appropriate medical use and NMUPO for pain relief was more prevalent among girls than boys. Multiple logistic regression analyses indicated that the odds of a positive screen for substance abuse in Year 2 were greater for adolescents who reported medical misuse or NMUPO for non-pain-relief motives in Year 1 compared with those who did not use prescription opioids. The findings indicate an increased risk for substance abuse among adolescents who report medical misuse or NMUPO for non-pain-relief motives over time. The findings have important clinical implications for interventions to reduce medical misuse and NMUPO among adolescents.

Factors Associated With History Of Non-Fatal Overdose Among Young Nonmedical Users Of Prescription Drugs. Silva K, Schrager SM, Kecojevic A, Lankenau SE. Drug Alcohol Depend. 2013; 128(1-2): 104-110.
The current study examines the prevalence and correlates of lifetime non-fatal overdose (OD) involving the nonmedical use of prescription opioids and tranquilizers among a sample of high-risk young adults in New York, NY and Los Angeles, CA. Data were derived from a cross-sectional study of 16-25 year old nonmedical users of prescription drugs (n=596). Unadjusted associations between OD history and socio-demographic and drug use variables were investigated in bivariate logistic regression models. Multivariate logistic regression models identified correlates of non-fatal OD. Lifetime prevalence of non-fatal overdose involving prescription opioids and/or tranquilizers was 23.6%. Factors associated with increased risk of non-fatal overdose included lower social class while growing up (OR: 1.81, 95% CI: [1.15, 2.83], $p<0.01$), having ever received care at a psychiatric hospital (OR: 1.79,

95% CI: [1.12, 2.85], p<0.05), ever witnessing a family member OD on drugs (OR: 1.59, 95% CI: [1.02, 2.50], p<0.05), being prescribed tranquilizers (OR: 2.07, 95% CI: [1.29, 4.27], p<0.01), ever snorting or sniffing opioids (OR: 2.51, 95% CI: [1.48, 4.27], p<0.001), injecting tranquilizers (OR: 3.09, 95% CI: [1.61, 5.93], p<0.001), and past 90-day injection drug use (OR: 1.68, 95% CI: [1.03, 2.74], p<0.05). Participants who reported past 90-day stimulant misuse had lower odds of reporting OD compared to those who were not recent stimulant users (OR: 0.60, 95% CI: [0.38-0.96], p<0.05).This study documents the high prevalence of experiencing non-fatal overdose among young nonmedical users of prescription drugs. Results could inform overdose prevention efforts throughout the U.S.

Discontinuous College Enrollment: Associations With Substance Use and Mental Health. Arria AM, Caldeira KM, Vincent KB, Winick ER, Baron RA, O'Grady KE. Psychiatr Serv. 2013; 64(2): 165-172.

This study examined the prospective relationship of substance use and mental health problems with risk of discontinuous enrollment in college. Participants were 1,145 students at a large public university who were interviewed annually for four years beginning at college entry in 2004 (year 1). Discontinuous enrollment was defined as a gap in enrollment of one or more semesters during the first two years (early discontinuity) or the second two years (late discontinuity) versus continuous enrollment throughout all four years. Explanatory variables measured in year 1 were scores on the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory, childhood conduct problems, cannabis use, number of illicit drugs used, and alcohol consumption. In years 3 and 4, participants reported lifetime history of clinically diagnosed attention-deficit hyperactivity disorder, depression, and anxiety, including age at diagnosis. Multinomial logistic regression models were developed to evaluate the association between the independent variables and discontinuous enrollment while holding constant background characteristics. Higher BDI scores predicted early discontinuity but not late discontinuity, whereas cannabis and alcohol use predicted only late discontinuity. Receiving a depression diagnosis during college was associated with both early and late discontinuity. Self-reported precollege diagnoses were not related to discontinuous enrollment once background characteristics were taken into account. Students who experience depressive symptoms or seek treatment for depression during college might be at risk of interruptions in their college enrollment. Cannabis use and heavy drinking appear to add to this risk. Students entering college with preexisting psychiatric diagnoses are not necessarily at risk of enrollment interruptions.

Playing Through Pain: Sports Participation and Nonmedical Use Of Opioid Medications Among Adolescents. Veliz PT, Boyd C, McCabe SE. Am J Public Health. 2013; 103(5): e28-30.

The authors assessed the nonmedical use of prescription opioids (NMUPO) among adolescents who participate in competitive sports. Using data from Monitoring the Future, they found that adolescent participants in high-injury sports had 50% higher odds of NMUPO than adolescents who did not participate in these types of sports (i.e., nonparticipants and participants in other sports). Detecting certain subpopulations of youths at risk for NMUPO should be a central concern among health care providers.

PREVENTION RESEARCH

Ecodevelopmental and Intrapersonal Moderators of a Family Based Preventive Intervention for Hispanic Youth: A Latent Profile Analysis. Prado G, Huang S, Cordova D, Malcolm S, Estrada Y, Cano N, Maldonado-Molina M, Bacio G, Rosen A, Pantin H, Brown C. Prev Sci. 2013; 14(3): 290-299.

Hispanic adolescents are disproportionately affected by externalizing disorders, substance use and HIV infection. Despite these health inequities, few interventions have been found to be efficacious for this population, and even fewer studies have examined whether the effects of such interventions vary as a function of ecodevelopmental and intrapersonal risk subgroups. The aim of this study was to determine whether and to what extent the effects of Familias Unidas, an evidence-based preventive intervention, vary by ecodevelopmental and intrapersonal risk subgroups. Data from 213 Hispanic adolescents (mean age=13.8, SD=0.76) who were enrolled in a randomized clinical trial evaluating the relative efficacy of Familias Unidas on externalizing disorders, substance use, and unprotected sexual behavior were analyzed. The results showed that Familias Unidas was efficacious over time, in terms of both externalizing disorders and substance use, for Hispanic youth with high family ecodevelopmental risk (e.g., poor parent-adolescent communication), but not with youth with moderate ecodevelopmental or low ecodevelopmental risk. The results suggest that classifying adolescents based on their family ecodevelopmental risk may be an especially effective strategy for examining moderators of family-based preventive interventions such as Familias Unidas. Moreover, these results suggest that Familias Unidas should potentially be targeted toward youth with high family ecodevelopmental risk. The utility of the methods presented in this article to other prevention scientists, including genetic, neurobiological and environmental scientists, is discussed.

Preventing High-Risk Sexual Behavior in Early Adulthood with Family Interventions in Adolescence: Outcomes and Developmental Processes. Caruthers A, Van Ryzin M, Dishion T. Prev Sci. 2013; DOI 10.1007/s11121-013-0383-9: 1-11.

Adolescent study participants who engaged in a brief, family-centered intervention (the Family Check-Up, FCU) were later assessed for the intervention's effects on high-risk sexual behavior (HRSB) in early adulthood (age 22). Participants (N=998 adolescents and their families) were randomly assigned to a family-centered intervention in sixth grade and were offered a gated, multilevel intervention that included (a) a school-based family resource center, (b) the FCU, and (c) more intensive, family-based treatment. All services were voluntary, but high-risk families were actively recruited into the FCU. Approximately 23% of the intervention families engaged in the FCU and approximately 18% engaged in more intensive treatment. Using an intent-to-treat design, we found that the direct effect of the FCU on HRSB was not significant; however, an analysis of the developmental processes indicated that intervention families demonstrated improved family relationship quality when compared to control families, which in turn resulted in lower levels of HRSB in early adulthood. Furthermore, the significant effect of family relationship quality on HRSB was mediated by differences in parental monitoring and early sexual activity, and these effects varied as a function of gender and ethnicity. Indirect effects of the FCU on HRSB were significant via multiple different pathways. The implications of these findings for enhancing the impact of family-centered interventions are discussed.

Attitude Ambivalence, Friend Norms, and Adolescent Drug Use. Hohman ZP, Crano WD, Siegel JT, Alvaro EM. Prev Sci. 2013.
This study assessed the moderating effects of attitudinal ambivalence on adolescent marijuana use in the context of the theory of planned behavior (TPB). With data from the National Survey of Parents and Youth (N = 1,604), two hierarchical multiple regression models were developed to examine the association of ambivalent attitudes, intentions, and later marijuana use. The first model explored the moderating effect of ambivalence on intentions to use marijuana; the second tested the moderation of ambivalence on actual marijuana use 1 year later. Results across both analyses suggest that ambivalence moderated the association of friend norms and subsequent adolescent marijuana use: friend norms were better predictors of marijuana intentions ($\beta = 0.151$, $t = 2.29$, $p = 0.02$) and subsequent use when adolescents were attitudinally ambivalent about marijuana use ($\beta = 0.071$, $t = 2.76$, $p = 0.006$). These results suggest that preventive programs that affect the certainty with which adolescents holds pro- or antimarijuana attitudes may influence the likelihood of their resistance to, initiation, or continuance of marijuana use.

Family Risk As A Predictor Of Initial Engagement and Follow-Through In A Universal Nurse Home Visiting Program To Prevent Child Maltreatment. Alonso-Marsden S, Dodge KA, O Donnell KJ, Murphy RA, Sato JM, Christopoulos C. Child Abuse Negl. 2013.
As nurse home visiting to prevent child maltreatment grows in popularity with both program administrators and legislators, it is important to understand engagement in such programs in order to improve their community-wide effects. This report examines family demographic and infant health risk factors that predict engagement and follow-through in a universal home-based maltreatment prevention program for new mothers in Durham County, North Carolina. Trained staff members attempted to schedule home visits for all new mothers during the birthing hospital stay, and then nurses completed scheduled visits three to five weeks later. Medical record data was used to identify family demographic and infant health risk factors for maltreatment. These variables were used to predict program engagement (scheduling a visit) and follow-through (completing a scheduled visit). Program staff members were successful in scheduling 78% of eligible families for a visit and completing 85% of scheduled visits. Overall, 66% of eligible families completed at least one visit. Structural equation modeling (SEM) analyses indicated that high demographic risk and low infant health risk were predictive of scheduling a visit. Both low demographic and infant health risk were predictive of visit completion. Findings suggest that while higher demographic risk increases families' initial engagement, it might also inhibit their follow-through. Additionally, parents of medically at-risk infants may be particularly difficult to engage in universal home visiting interventions. Implications for recruitment strategies of home visiting programs are discussed.

Reductions in HIV/STI Incidence and Sharing of Injection Equipment among Female Sex Workers who Inject Drugs: Results from a Randomized Controlled Trial. Strathdee S, Abramovitz D, Lozada R, Martinez G, Rangel MG, Vera A, Staines H, Mages-Rodriguez C, Patterson TL. PLoS One. 2013; Epub.
The authors evaluated brief combination interventions to simultaneously reduce sexual and injection risks among female sex workers who inject drugs (FSW-IDUs) in Tijuana and Ciudad (Cd.) Juarez, Mexico during 2008-2010, when harm reduction coverage was expanding rapidly in Tijuana, but less so in Cd. Juarez. FSW-IDUs >18 years reporting sharing

injection equipment and unprotected sex with clients within the last month participated in a randomized factorial trial comparing four brief, single-session conditions combining either an interactive or didactic version of a sexual risk intervention to promote safer sex in the context of drug use, and an injection risk intervention to reduce sharing of needles/injection paraphernalia. Women underwent quarterly interviews and testing for HIV, syphilis, gonorrhea, Chlamydia and Trichomonas, blinding interviewers and assessors to assignment. Poisson regression with robust variance estimation and repeated measures ordinal logistic regression examined effects on combined HIV/STI incidence and receptive needle sharing frequency, respectively. Of 584 initially HIV-negative FSW-IDUs, retention was ≥90%. After 12 months, HIV/STI incidence decreased >50% in the interactive vs. didactic sex intervention (Tijuana:AdjRR:0.38, 95%CI:0.16-0.89; Juarez: AdjRR:0.44,95%CI:0.19-0.99). In Cd. Juarez, women receiving interactive vs. didactic injection risk interventions decreased receptive needle-sharing by 85% vs. 71%, respectively (p=0.04); in Tijuana, receptive needle sharing declined by 95%, but was similar in active versus didactic groups. Tijuana women reported significant increases in access to syringes and condoms, but Juarez women did not. The authors conclude that after 12 months in both cities, the interactive sexual risk intervention significantly reduced HIV/STI incidence. Expanding free access to sterile syringes coupled with brief, didactic education on safer injection was both necessary and sufficient in achieving robust, sustained injection risk reductions in Tijuana. In the absence of expanding syringe access in Cd. Juarez, the injection risk intervention achieved significant, albeit more modest reductions, suggesting that community-level interventions incorporating harm reduction are more powerful than individual-level interventions.

Direct and Indirect Effects of a Family-Based Intervention in Early Adolescence on Parent-Youth Relationship Quality, Late Adolescent Health, and Early Adult Obesity.
Van Ryzin M, Nowicka P. J Fam Psychol. 2013; 27(1): 106-116.
The authors explored family processes in adolescence that may influence the likelihood of obesity in early adulthood using a randomized trial of a family-based intervention (the Family Check-Up, or FCU). The FCU has been shown to reduce escalations in antisocial behavior and depression in adolescence by supporting positive family management practices, but no research has examined the mechanisms by which the FCU could influence health-related attitudes and behaviors linked to obesity. Participants were 998 adolescents (n = 526 male; n = 423 European American; M age 12.21 years) and their families, recruited in 6th grade from 3 middle schools in the Pacific Northwest. The authors used structural equation modeling (SEM) and an Intent-To-Treat (ITT) design to evaluate the direct and indirect effects of the FCU on parent-youth relationship quality (ages 12-15), healthy lifestyle behaviors, eating attitudes, depressive symptoms (all measured at age 17), and obesity (age 22). They found that the FCU led to greater parent-youth relationship quality, which predicted enhanced health-related behaviors, reduced maladaptive eating attitudes, and reduced depression. In turn, reduced maladaptive eating attitudes predicted reduced odds of obesity. The indirect effect of the FCU on obesity by way of parent-youth relationship quality and eating attitudes was significant. These findings illustrate how family processes may influence adolescent health and suggest that family functioning may be an additional factor to consider when developing intervention programs for obesity.

The Evaluation of Two First-Grade Preventive Interventions on Childhood Aggression and Adolescent Marijuana Use: A Latent Transition Longitudinal Mixture Model. Liu W, Lynne-Landsman S, Petras H, Masyn K, Ialongo N. Prev Sci. 2013; 14: 206-217.
Aggressive, disruptive behavior during early childhood has been linked to a number of later negative outcomes, one of them being adolescent marijuana use. This study evaluates the impact of two first-grade universal interventions (classroom-centered and family-school partnership) on the development of aggression in early childhood (grades 1-3) and marijuana use in adolescence (grades 8-12) via a latent transition longitudinal mixture model. For males, despite the significant proximal impact of the classroom-centered intervention on trajectory class membership of early childhood aggression, as well as the significant association between aggression trajectory class membership and marijuana use longitudinal latent class membership, the predicted probabilities of being in the high frequency marijuana use class did not differ significantly by intervention status, though in the expected direction. Associations for females are limited to the proximal impact of the classroom-centered intervention on trajectory class membership of aggression. This study extends the prior work of Petras et al. (Prev Sci 12:300-313, 2011) by considering that aggressive, disruptive behavior during early childhood is linked not only to adolescent aggressive, disruptive behavior (i.e., homotypic continuity) but also to adolescent marijuana use (i.e., heterotypic continuity) and by considering that an early intervention may influence later non-targeted behaviors through these heterotypic developmental pathways. Implications for developmental theories and substance abuse prevention are discussed.

The Use of Multiple Versus Single Assessment Time Points to Improve Screening Accuracy in Identifying Children at Risk for Later Serious Antisocial Behavior. Petras H, Buckley J, Leoutsakos J, Stuart E, Ialongo N. Prev Sci. 2013; DOI 10.1007/s11121-012-0324-z: 1-14.
Guided by Kraemer et al.'s (Psychological Methods, 3:257-271, 1999) framework for measuring the potency of risk factors, the authors sought to improve on the classification accuracy reported in Petras et al. (Journal of the American Academy of Child and Adolescent Psychiatry 43:88-96, 2004a) and Petras et al. (Journal of the American Academy of Child and Adolescent Psychiatry 44:790-797, 2005) by using multiple as opposed to single point in time assessments of early aggressive and disruptive behavior in the classification of youth who would likely benefit from targeted preventive interventions. Different from Petras et al. (2004a, 2005), the outcome used in this study included serious antisocial behavior in young adulthood as well as in adolescence. Among males, the use of multiple time points did not yield greater classification accuracy than the highest single time points, that is, third and fifth grades. For females, although fifth grade represented the best single time point in terms of classification accuracy, no significant association was found between earlier time points and the later outcome, rendering a test of the multiple time points hypothesis moot. The findings presented in this study have strong implications for the design of targeted intervention for violence prevention, indicating that the screening quality based on aggression ratings during the elementary years is rather modest, particularly for females.

Children with Co-occurring Academic and Behavior Problems in First Grade: Distal Outcomes in Twelfth Grade. Darney D, Reinke W, Herman K, Stormont M, Ialongo N. J Sch Psychol. 2013; 51(1): 117-128.
The aim of the current study was to evaluate the eleven year longitudinal association between students identified in first grade as having academic and behavior problems and distal outcomes in twelfth grade. The study extends prior research that identified latent classes of academic and behavior problems in a longitudinal community sample of 678 predominately African American first-grade students. The type and number of classes identified in first grade differed by gender, but results indicated that students within the classes of behavior and academic problems had long-term negative outcomes in the twelfth grade. The class with co-occurring academic and behavior problems in first grade had the greatest risk for negative distal outcomes for both boys and girls including higher likelihood of special education placement, mental health service use, poor academic achievement, and school dropout. Implications for prevention, early intervention, and current practices in schools are discussed.

Does a Booster Intervention Augment the Preventive Effects of an Abbreviated Version of the Coping Power Program for Aggressive Children? Lochman J, Baden R, Boxmeyer C, Powell N, Qu L, Salekin K, Windle M. J Abnorm Child Psychol. 2013 Feb 16; E-pub ahead of print.
Booster interventions have been presumed to be important methods for maintaining the effects of evidence-based programs for children with behavioral problems, but there has been remarkably little empirical attention to this assumption. The present study examines the effect of a child-oriented booster preventive intervention with children who had previously received an abbreviated version (24 child sessions, 10 parent sessions) of the Coping Power targeted prevention program. Two hundred and forty-one children (152 boys, 89 girls) were screened as having moderate to high levels of aggressive behavior in 4th grade, then half were randomly assigned to receive the abbreviated Coping Power program in 5th grade, and half of the preventive intervention children were then randomly assigned to a Booster condition in 6th grade. The Booster sessions consisted of brief monthly individual contacts, and were primarily with the children. Five assessments across 4 years were collected from teachers, providing a three-year follow-up for all children who participated in the project. Results indicated that the abbreviated Coping Power program (one-third shorter than the full intervention) had long-term effects in reducing children's externalizing problem behaviors, proactive and reactive aggression, impulsivity traits and callous-unemotional traits. The Booster intervention did not augment these prevention effects. These findings indicate that a briefer and more readily disseminated form of an evidence-based targeted preventive intervention was effective. The findings have potential implications for policy and guidelines about possible intervention length and booster interventions.

Changes in Friends' and Parental Influences on Cigarette Smoking From Early Through Late Adolescence. Liao Y, Huang Z, Huh J, Pentz M, Chou C. J Adolesc Health. 2013; http://dx.doi.org/10.1016/ j.jadohealth.2013.01.020: 1-7.
This study examined the changes in friends' and parental influences on cigarette smoking across two developmentally distinct social environments for adolescents: junior high school and high school. Longitudinal data consisting of seven repeated measures following 1,001 adolescents from 7th to 12th grade was obtained from the Midwestern Prevention Project. A

two-piece Growth Curve Model (GCM) was used to assess the growth trajectory of current cigarette use: one piece for the junior high school period, and the other for the high school period. Perceived friends' and parental cigarette use were each used as a time-varying covariate in separate GCMs. Effects of friends' and parental cigarette use remained significant on adolescent cigarette smoking across the two developmental periods. The magnitude of friends' effect was in general higher during junior high school than high school. The magnitude of the parental effect remained relatively stable between the two periods. However, decreasing trends in both effects were observed from 10th to 12th grade. Gender differences also emerged. Friends' and parental effects were greater for girls in their early high school years, whereas friends' effect decreased in magnitude among girls and increased among boys during high school. The authors conclude that the transition from junior high school to high school represents an opportunity for interventions to counteract peer influence given that such influence appeared to be much weaker during this period. However, interventions should continue to target parents as their behavior remains influential through the end of high school.

Dimensions of Callousness In Early Childhood: Links To Problem Behavior and Family Intervention effectiveness. Hyde L, Shaw D, Gardner F, Cheong J, Dishion T, Wilson M. Dev Psychopathol. 2013; 25(2): 347-363.

This study examined dimensions of callous behaviors in early childhood and the role of these behaviors in the development of conduct problems, as well as responsiveness to a family-centered preventative intervention. Caregiver reports of callous behaviors were examined using exploratory and confirmatory factor analysis. Problem behavior was examined using within- and cross-informant reports of these behaviors. Parenting was measured using observational methods within the context of a randomized control trial of the Family Check-Up with a sample of 731 ethnically diverse boys and girls (followed from ages 2 to 4) at high risk for later conduct problems. Results demonstrated that a measure of deceitful-callous (DC) behaviors had acceptable factor loadings and internal consistency at ages 3 and 4. DC behaviors at age 3 predicted problem behavior concurrently and longitudinally within and across informant. However, DC behaviors did not reduce the effectiveness of the family preventative intervention. These findings have implications for our understanding of behaviors that may precede later callous-unemotional traits and for our understanding of the development and prevention of early starting conduct problems.

Social Identity as a Moderator of the Association Between Perceived Norms and Marijuana Use. Neighbors C, Foster D, Walker D, Kilmer J, Lee C. J Stud Alcohol Drugs. 2013; 74(3): 479-483.

This study extends previous examinations of social influences and marijuana use in considering how heavy marijuana users view themselves relative to their peers. The authors were specifically interested in evaluating whether (a) heavy-using marijuana users would identify more strongly with other users than with typical students, (b) identification with other marijuana users would be more strongly associated with own use, and (c) the association between perceived norms and marijuana use would be moderated by identification with peers. Participants were 107 heavy (five or more times per month) marijuana users who completed an online survey assessing perceived norms for marijuana use, identification with typical students and other marijuana-using students, and marijuana use (frequency of use, joints per week, and hours high). Participants unexpectedly identified more strongly with typical students rather

than with other marijuana-using students. Identification with other marijuana users was, however, associated with more use. In addition, perceived norms were associated with more use but primarily among those who identified more with other users but not with typical students. The authors conclude that heavy marijuana users may be reluctant to identify themselves as users and may prefer to think of themselves as typical students. This may provide clinical opportunities to highlight discrepancies. In addition, identification with other users and lack of identification with typical students may be risk factors for heavier use and good indicators of candidacy for norms-based interventions. In sum, the present findings extend our understanding of the influence of social identity among young adult marijuana users and suggest novel directions for intervention strategies.

Measuring Fidelity and Adaptation: Reliability of a Instrument for School-Based Prevention Programs. Bishop D, Pankratz M, Hansen W, Albritton J, Albritton L, Strack J. Eval Health Prof. 2013 Feb 19; Epub ahead of print.
There is a need to standardize methods for assessing fidelity and adaptation. Such standardization would allow program implementation to be examined in a manner that will be useful for understanding the moderating role of fidelity in dissemination research. This article describes a method for collecting data about fidelity of implementation for school-based prevention programs, including measures of adherence, quality of delivery, dosage, participant engagement, and adaptation. The authors report about the reliability of these methods when applied by four observers who coded video recordings of teachers delivering All Stars, a middle school drug prevention program. Interrater agreement for scaled items was assessed for an instrument designed to evaluate program fidelity. Results indicated sound interrater reliability for items assessing adherence, dosage, quality of teaching, teacher understanding of concepts, and program adaptations. The interrater reliability for items assessing potential program effectiveness, classroom management, achievement of activity objectives, and adaptation valences was improved by dichotomizing the response options for these items. The item that assessed student engagement demonstrated only modest interrater reliability and was not improved through dichotomization. Several coder pairs were discordant on items that overall demonstrated good interrater reliability. Proposed modifications to the coding manual and protocol are discussed.

Some Methodological Considerations In Theory-Based Health Behavior Research. Collins L, Mackinnon D, Reeve B. Health Psychol. 2013; 32(5): 586-591.
As this special issue shows, much research in social and personality psychology is directly relevant to health psychology. In this brief commentary, the authors discuss three topics in research methodology that may be of interest to investigators involved in health-related psychological research. The first topic is statistical analysis of mediated and moderated effects. The second is measurement of latent constructs. The third is the Multiphase Optimization Strategy, a framework for translation of innovations from social and personality psychology into behavioral interventions.

Multiple Behavior Interventions to Prevent Substance Abuse and Increase Energy Balance Behaviors in Middle School Students. Velicer W, Redding C, Paiva A, Mauriello L, Blissmer B, Oatley K, Meier K, Babbin S, McGee H, Prochaska J, Burditt C, Fernandez A. Transl Behav Med. 2013; 3(1): 82-93.

This study examined the effectiveness of two transtheoretical model-tailored, computer-delivered interventions designed to impact multiple substance use or energy balance behaviors in a middle school population recruited in schools. Twenty middle schools in Rhode Island including sixth grade students (N=4,158) were stratified and randomly assigned by school to either a substance use prevention (decreasing smoking and alcohol) or an energy balance (increasing physical activity, fruit and vegetable consumption, and limiting TV time) intervention group in 2007. Each intervention involved five in-class contacts over a 3-year period with assessments at 12, 24, and 36 months. Main outcomes were analyzed using random effects modeling. In the full energy balance group and in subsamples at risk and not at risk at baseline, strong effects were found for physical activity, healthy diet, and reducing TV time, for both categorical and continuous outcomes. Despite no direct treatment, the energy balance group also showed significantly lower smoking and alcohol use over time than the substance use prevention group. The energy balance intervention demonstrated strong effects across all behaviors over 3 years among middle school students. The substance use prevention intervention was less effective than the energy balance intervention in preventing both smoking and alcohol use over 3 years in middle school students. The lack of a true control group and unrepresented secular trends suggest the need for further study.

Sex Risk Behavior Among Adolescent and Young Adult Children of Opiate Addicts: Outcomes From the Focus on Families Prevention Trial and an Examination of Childhood and Concurrent Predictors of Sex Risk. Skinner ML, Fleming CB, Haggerty KP, Catalano RF. Prev Sci. 2013; DOI 10.1007/s11121-012-0327-9 1-8.

This study reports on rates and predictors of sex risk behavior among a sample of adolescent and young adult children of parents enrolled in methadone treatment for opiate addiction. Data are from 151 participants (80 males, 71 females) in the Focus on Families (FOF) project, a randomized trial of a family intervention and a study of the development of at-risk children. The study participants are children of parents enrolled in methadone treatment between 1990 and 1993. Participants were interviewed in 2005 when they ranged in age from 15 to 29 years. In the year prior to the follow-up, 79 % of the males and 83 % of females were sexually active, 26 % of males and 10 % of females had more than one partner in the prior year, and 34 % of males and 24 % of females reported having sex outside of a committed relationship. Twenty-four percent of males and 17 % of females met criteria for high-risk sexual behavior, reporting casual or multiple partners in the prior year and inconsistent condom use. Participants in the intervention and control conditions did not differ significantly in terms of any measure of sex risk behavior examined. None of the measures of parent behavior and family processes derived from data at baseline of the FOF study predicted whether participants engaged in high-risk sex. Among measures derived from data collected at long-term follow-up, however, having ever met criteria for substance abuse or dependence predicted greater likelihood of high-risk sexual behavior, and being married or being in a romantic relationship was associated with lower likelihood of high-risk sexual behavior. The findings point to the important role of committed relationships in regulating sex risk behavior among this population, as well as heightened levels of sex risk behavior associated with substance abuse or dependence.

A Randomized Trial Of A Behavioral Intervention For High Risk Substance-Using MSM. Kurtz SP, Stall RD, Buttram ME, Surrat HE, Chen M. AIDS Behav. 2013; Epub.
Substance-using men who have sex with men (MSM) are among the groups at highest risk for HIV infection in the United States. The authors report the results of a randomized trial testing the efficacy of a small group sexual and substance use risk reduction intervention based on empowerment theory compared to an enhanced efficacious control condition among 515 high risk not-in-treatment MSM substance users. Effect sizes for sexual risk and substance use outcomes were moderate to large: HIV transmission risk frequency, d = 0.71 in the control versus 0.66 in the experimental group; number of anal sex partners, d = 1.04 versus 0.98; substance dependence symptoms, d = 0.49 versus 0.53; significant differences were not observed between conditions. Black MSM reduced their risks at a greater rate than White or Latino men. The findings point to a critically important research agenda to reduce HIV transmission among MSM substance users.

Alcohol and Drug Use Among Young Adults Driving To A Drinking Location. Voas R, Johnson M, Miller B. Drug Alcohol Depend. 2013; Epub.
Clubs that feature electronic music dance events (EMDEs) draw young adults aged 18-34 who are at high-risk for alcohol-related crashes to locations where alcohol sales are the principal source of revenue. Up to 30% of these attendees may also use drugs. This provides an important context in which to study driving arrangements that reflect concern with impaired driving. The authors explored whether drivers were using less alcohol and fewer drugs at exit than their passengers were and whether a driver for the group ever changed after consuming too much during the evening. Using biological measures of alcohol consumption (breath tests) and drug use (oral fluid tests), 175 drivers and 272 passengers were surveyed among young adults arriving at and departing from EMDEs in San Francisco. Upon exit from the drinking locations, only 20% of the drivers, compared to 47% of the passengers, had a high breath alcohol concentration (defined as a BrAC of .05g/dL or greater). Further, there was evidence that drivers with high BrACs switched to passenger status on exit and former passengers with lower BrACs replaced those drivers. However, there were no differences in the prevalence of drug use among drivers and passengers. These findings suggest that the effort by young adult drivers to avoid alcohol-impaired driving appears to be reducing the number of drivers with high BrACs returning from drinking locations, such as EMDEs, by about one third. However, there is no similar pattern for drugged driving.

The Link Between Harsh Home Environments and Negative Academic Trajectories Is Exacerbated By Victimization In The Elementary School Peer Group. Schwartz D, Lansford J, Dodge K, Pettit G, Bates J. Dev Psychol. 2013; 49(2): 305-316.
This article presents a prospective investigation focusing on the moderating role of peer victimization on associations between harsh home environments in the preschool years and academic trajectories during elementary school. The participants were 388 children (198 boys, 190 girls) who we recruited as part of an ongoing multisite longitudinal investigation. Preschool home environment was assessed with structured interviews and questionnaires completed by parents. Peer victimization was assessed with a peer nomination inventory that was administered when the average age of the participants was approximately 8.5 years. Grade point averages (GPAs) were obtained from reviews of school records, conducted for 7 consecutive years. Indicators of restrictive punitive discipline and exposure to violence were

associated with within-subject declines in academic functioning over 7 years. However, these effects were exacerbated for those children who had also experienced victimization in the peer group during the intervening years.

The Influence Of Having Children On HIV-Related Risk Behaviors Of Female Sex Workers and Their Intimate Male Partners In Two Mexico-US Border Cities. Rolon M, Syvertsen J, Robertson A, Rangel M, Martinez G, Ulibarri M, Servin A, Strathdee S. J Trop Pediatr. 2013; 59(3): 214-219.
Among female sex workers who use drugs, the experience of having children and its effect on HIV risk behaviors remains underexplored. The authors draw from a study of 214 female sex workers and their intimate non-commercial partners in Tijuana and Ciudad Juárez, México (n = 428), approximately 30% of whom have children living with them. During qualitative interviews with 41 of these couples, having children emerged as an important topic. Children influenced partners' lives and HIV-related risk behaviors in positive and negative ways. Couples perceived that children strengthened their relationships. Concern for children's well-being motivated couples to contemplate healthier lifestyle changes. However, childrearing costs motivated sex work and structural constraints prevented couples from enacting lifestyle changes. Case studies illustrate these themes and highlight implications for couple- and family-based harm reduction interventions. Specifically, these results suggest a need for economic alternatives to sex work while working with families to develop risk reduction skills.

Toward Population Impact from Home Visiting. Dodge K, Goodman W, Murphy R, O 'Donnell K, Sato J. Zero Three. 2013; 33(3): 17-23.
Although some home-visiting programs have proven effective with the families they serve, no program has yet demonstrated an impact at the population level. The authors describe the Durham Connects (DC) initiative, which aims to achieve population impact by coalescing community agencies to serve early-intervention goals through a Preventive System Of Care and by delivering a universal, short-term, postnatal nurse home-visiting program. The home-visitor delivers brief intervention, assesses family needs in 12 domains, and connects the family with community resources to address individualized family needs. Evaluation of DC occurred through a population randomized controlled trial of all 4,777 births in Durham, NC, over an 18-month period. DC was implemented with high penetration and high fidelity. Impact evaluation indicated that by age 6 months, DC infants had 18 percent fewer emergency room visits and 80 percent fewer overnights in the hospital than did control families. The authors conclude that population impact is achievable if a program attends to challenges of community partnership, universal reach and assessment, rigorous evaluation, and models for sustaining funding.

Meta-Analysis and Subgroups. Borenstein M, Higgins JPT. Prev Sci. 2013; 14(2): 134-143.
Subgroup analysis is the process of comparing a treatment effect for two or more variants of an intervention-to ask, for example, if an intervention & impact is affected by the setting (school versus community), by the delivery agent (outside facilitator versus regular classroom teacher), by the quality of delivery, or if the long-term effect differs from the short-term effect. While large-scale studies often employ subgroup analyses, these analyses cannot generally be performed for small-scale studies, since these typically include a homogeneous population and only one variant of the intervention. This limitation can be bypassed by using meta-analysis.

Meta-analysis allows the researcher to compare the treatment effect in different subgroups, even if these subgroups appear in separate studies. The authors discuss several statistical issues related to this procedure, including the selection of a statistical model and statistical power for the comparison. To illustrate these points, they use the example of a meta-analysis of obesity prevention.

School Outcomes Of Aggressive-Disruptive Children: Prediction From Kindergarten Risk Factors and Impact Of the Fast Track Prevention Program. Bierman K, Coie J, Dodge K, Greenberg M, Lochman J, McMohan R, Pinderhughes E, Pinderhughes E. Aggress Behav. 2013; 39(2): 114-130.
A multi-gate screening process identified 891 children with aggressive-disruptive behavior problems at school entry. Fast Track provided a multi-component preventive intervention in the context of a randomized-controlled design. In addition to psychosocial support and skill training for parents and children, the intervention included intensive reading tutoring in first grade, behavioral management consultation with teachers, and the provision of homework support (as needed) through tenth grade. This study examined the impact of the intervention, as well as the impact of the child 's initial aggressive-disruptive behaviors and associated school readiness skills (cognitive ability, reading readiness, attention problems) on academic progress and educational placements during elementary school (Grades 1-4) and during the secondary school years (Grades 7-10), as well as high school graduation. Child behavior problems and skills at school entry predicted school difficulties (low grades, grade retention, placement in a self-contained classroom, behavior disorder classification, and failure to graduate). Disappointingly, the intervention did not significantly improve these long-term school outcomes.

Predictors of Engagement in a School-Based Family Preventive Intervention for Youth Experiencing Behavioral Difficulties. Ellis M, Lindsey M, Barker E, Boxmeyer C, Lochman J. Prev Sci. 2013; Epub.
The researchers longitudinally assessed parent and child levels of engagement in an evidence-based preventive intervention for children. The sample included 114 fifth graders with aggressive, disruptive behaviors and their parents who participated in the Coping Power Program. Findings indicate that levels of engagement differentially fluctuated for children and parents throughout the course of the intervention. Results also suggest that child levels of engagement early in the course of the program influenced parent mid-intervention levels of engagement. Further, these relationships persisted when the influence of family environment variables were included in analyses.

Youth Aggressive/Disruptive Behavior Trajectories and Subsequent Gambling Among Urban Male Youth. Martins S, Liu W, Hedden S, Goldweber A, Storr C, Derevensky J, Stinchfield R, Ialongo N, Petras H. J Clin Child Adolesc Psychol. 2013; DOI: 10.1080/15374416.2013.764827;
1-12.
This study examines the association between aggressive/disruptive behavior development in two distinct developmental periods-childhood (i.e., Grades 1-3) and early adolescence (i.e., Grades 6-10)-and subsequent gambling behavior in late adolescence up to age 20. The sample consists of 310 urban males of predominately minority and low socioeconomic status followed

from first grade to late adolescence. Separate general growth mixture models were estimated to explore the heterogeneity in aggressive/disruptive behavior development in the aforementioned two periods. Three distinct behavior trajectories were identified for each period: a chronic high, a moderate increasing, and a low increasing class for childhood, and a chronic high, a moderate increasing, followed by decreasing and a low stable class for early adolescence. There was no association between childhood behavior trajectories and gambling involvement. Males with a moderate behavior trajectory in adolescence were two times more likely to gamble compared to those in the low stable class (OR = 1.89, 95% CI = 1.11, 3.24). Those with chronic high trajectories during either childhood or early adolescence (OR = 2.60, 95% CI = 1.06, 6.38; OR = 3.19, 95% CI = 1.18, 8.64, respectively) were more likely to be at-risk/problem gamblers than those in the low class. Aggressive/disruptive behavior development in childhood and early adolescence is associated with gambling and gambling problems in late adolescence among urban male youth. Preventing childhood and youth aggressive/disruptive behavior may be effective to prevent youth problem gambling.

Substance Use Among Women Receiving Post-Rape Medical Care, Associated Post-Assault Concerns and Current Substance Abuse: Results From A National Telephone Household Probability Sample. McCauley J, Kilpatrick D, Walsh K, Resnick H. Addict Behav. 2013; 38(4): 1952-1957.

The aim of this study was to examine post-rape substance use, associated post rape medical and social concern variables, and past year substance abuse among women reporting having received medical care following a most recent or only lifetime incident of rape. Using a subsample of women who received post-rape medical care following a most recent or only rape incident (n=104) drawn from a national household probability sample of U.S. women, the current study described the extent of peritraumatic substance use, past year substance misuse behaviors, post-rape HIV and pregnancy concerns, and lifetime mental health service utilization as a function of substance use at time of incident. One-third (33%) of women seeking post-rape medical attention reported consuming alcohol or drugs at the time of their rape incident. Nearly one in four (24.7%) and one in seven (15%) women seeking medical attention following their most recent rape incident endorsed drug (marijuana, illicit, non-medical use of prescription drugs, or club drug) use or met substance abuse criteria, respectively, in the past year. One in twelve (8.4%) women reported at least monthly binge drinking in the past year. Approximately two-thirds of women reported seeking services for mental health needs in their lifetime. Post-rape concerns among women reporting peritraumatic substance use were not significantly different from those of women not reporting such use. The authors conclude that substance use was reported by approximately one-third of women and past year substance abuse was common among those seeking post-rape medical care. Implications for service delivery, intervention implementation, and future research are discussed.

Environmental Influences Associated with Gambling in Young Adulthood. Martins S, Storr C, Lee G, Ialongo N. J Urban Health. 2013; 90(1): 130-140.

Social and environmental influences on gambling behavior are important to understand because localities can control the sanction and location of gambling opportunities. This study explores whether neighborhood disadvantage is associated with gambling among predominantly low-income, urban young adults and to explore if differences in physical vs.

compositional aspects of the neighborhood can be found. Data are from a sample of 596 young adults interviewed when they were 21-22 years, who have been participating in a longitudinal study since entering first grade in nine public US Mid-Atlantic inner-city schools (88 % African Americans). Data were analyzed via factor analysis and logistic regression models. One third of the sample (n=187) were past-year gamblers, 42 % of them gambled more than once a week, and 31 % had gambling-related problems. Those living in moderate and high disadvantaged neighborhoods were significantly more likely to be past-year gamblers than those living in low disadvantaged neighborhoods. Those living in high disadvantaged neighborhoods were ten times more likely than those living in low disadvantaged neighborhoods to have gambling problems. Factor analysis yielded a 2-factor model, an "inhabitant disadvantage factor" and a "surroundings disadvantage factor." Nearly 60 % of the sample lived in neighborhoods with high inhabitants disadvantage (n=375) or high surroundings disadvantage (n=356). High inhabitants disadvantage was associated with past-year frequent gambling (odds ratios (aOR) =2.26 (1.01, 5.02)) and gambling problems (aOR=2.81 (1.18, 6.69)). Higher neighborhood disadvantage, particularly aspects of the neighborhood concerning the inhabitants, was associated with gambling frequency and problems among young adult gamblers from an urban, low-income setting.

Parent and Peer Predictors of Violent Behavior of Black and White Teens. Haggerty K, Skinner M, McGlynn-Wright A, Catalano R, Crutchfield R. Violence Vict. 2013; 28(1): 145-160.

This study examines the role that parenting and deviant peers play on frequency of self-reported violent behavior in the 10th grade while testing race differences in mean levels and impact of these risk and protective factors. The level and impact of family and peer factors on violent behavior across race are modeled prospectively from 8th to 10th grade in a sample of 331 (Black [n = 163], White [n = 168]) families from Seattle, Washington, using data from self-administered computer-assisted questionnaires. Mean-level differences indicated greater levels of violent behavior and risk for Black teens in some cases and higher protection in others. Multiple-group structural equation modeling indicated no race differences in predictors of teen violence. Income was also predictive of violent behavior, but analyses including both income and race indicated their relationships to violence overlapped so neither was uniquely predictive. Subsequent logistic regressions revealed that both race and income differences in violent behavior were mediated by association with friends who get in serious trouble at school. The authors conclude that higher rates of self-reported violent behavior by Blacks compared to Whites are attributable to lower family income and higher rates of associating with deviant peers at school.

A Dual-Process Model of Early Substance Use: Tests in Two Diverse Populations of Adolescents. Wills T, Bantum E, Pokhrel P, Maddock J, Ainette M, Morehouse E, Fenster B. Health Psychol. 2013; 32(5): 533-542.

The authors tested a dual-process model based on behavioral and emotional regulation constructs, which posits that good self-control and poor regulation make independent contributions and have different types of pathways to outcomes. The utility of the model for predicting substance use was tested in two diverse populations of younger adolescents. A survey was administered in classrooms to middle-school students in Westchester County, New York (N = 601) and Honolulu, Hawaii

(N = 881). The New York sample was 8% African American, 5% Asian American, 47% Caucasian, 31% Hispanic, and 9% other ethnicity. The Hawaii sample was 21% Asian American, 8% Caucasian, 26% Native Hawaiian/Pacific Islander, 34% Filipino, and 10% other ethnicity. Structural equation modeling analyses tested pathways from the four regulation variables through six hypothesized mediators to a criterion construct of substance use (tobacco, alcohol, and marijuana). Results were replicated across samples and were consistent with prediction. Unique contributions were found for good self-control and poor regulation, including both behavioral and emotional aspects. Good self-control had an inverse effect on substance use primarily through relations to higher levels of protective factors (e.g., academic competence). Poor regulation independently had a risk-promoting effect on substance use through relations to higher levels of risk factors (e.g., negative life events). Two field studies showed the dual-process model is robust across different populations. Substance prevention programs should consider approaches for enhancing good self-control as well as procedures for reducing poor regulation and minimizing its impact. Extensions to health behaviors including dietary intake and physical activity are discussed.

The Ecology of Early Childhood Risk: A Canonical Correlation Analysis of Children's Adjustment, Family, and Community Context in a High-Risk Sample. Vilsaint C, Aiyer S, Wilson M, Shaw D, Dishion T. J Prim Prev. 2013 Aug; 34(4): 261-277.
The ecology of the emergence of psychopathology in early childhood is often approached by the analysis of a limited number of contextual risk factors. In the present study, the authors provide a comprehensive analysis of ecological risk by conducting a canonical correlation analysis of 13 risk factors at child age 2 and seven narrow-band scales of internalizing and externalizing problem behaviors at child age 4, using a sample of 364 geographically and ethnically diverse, disadvantaged primary caregivers, alternative caregivers, and preschool-age children. Participants were recruited from Special Supplemental Nutrition Program for Women, Infants, and Children sites and were screened for family risk. Canonical correlation analysis revealed that (1) a first latent combination of family and individual risks of caregivers predicted combinations of child emotional and behavioral problems, and that (2) a second latent combination of contextual and structural risks predicted child somatic complaints. Specifically, (1) the combination of chaotic home, conflict with child, parental depression, and parenting hassles predicted a co-occurrence of internalizing and externalizing behaviors, and (2) the combination of father absence, perceived discrimination, neighborhood danger, and fewer children living in the home predicted child somatic complaints. The research findings are discussed in terms of the development of psychopathology, as well as the potential prevention needs of families in high-risk contexts.

Effects of Video Feedback on Early Coercive Parent-Child Interactions: The Intervening Role of Caregivers' Relational Schemas. Smith J, Dishion T, Moore K, Shaw D. J Clin Child Adolesc Psychol. 2013; 42(3): 405-417.
The authors examined the effect of adding a video feedback intervention component to the assessment feedback session of the Family Check-Up (FCU) intervention (Dishion & Stormshak, 2007). They hypothesized that the addition of video feedback procedures during the FCU feedback at child age 2 would have a positive effect on caregivers' negative relational schemas of their child, which in turn would mediate reductions in observed coercive caregiver-child interactions assessed at age 5. The authors observed the caregiver-child interaction

videotapes of 79 high-risk families with toddlers exhibiting clinically significant problem behaviors. A quasi-random sample of families was provided with direct feedback on their interactions during the feedback session of the FCU protocol. Path analysis indicated that reviewing and engaging in feedback about videotaped age 2 assessment predicted reduced caregivers' negative relational schemas of the child at age 3, which acted as an intervening variable on the reduction of observed parent-child coercive interactions recorded at age 5. Video feedback predicted improved family functioning over and above level of engagement in the FCU in subsequent years, indicating the important incremental contribution of using video feedback procedures in early family-based preventive interventions for problem behaviors. Supportive video feedback on coercive family dynamics is an important strategy for promoting caregiver motivation to reduce negative attributions toward the child, which fuel coercive interactions. Our study also contributes to the clinical and research literature concerning coercion theory and effective intervention strategies by identifying a potential mechanism of change.

Collateral Benefits of the Family Check-up In Early Childhood: Primary Caregivers' Social Support and Relationship Satisfaction. McEachern A, Fosco G, Dishion T, Shaw D, Wilson M, Gardner F. J Fam Psychol. 2013; 27(2): 271-281.
This research investigated potential collateral benefits of the Family Check-Up (FCU) intervention, namely, primary caregivers' perceived social support and couple relationship satisfaction. A subsample of 435 low-income families with a 2-year-old child was recruited to participate in a randomized controlled trial assessing preventative effects of the FCU. Longitudinal growth models were used to evaluate intention-to-treat effects of the FCU on increases in primary caregiver's ratings of social support satisfaction with perceived social support and significant-other relationships, and indirect effects on primary caregivers through improvements in children's behavior problems. Support was found for a model in which reductions in child problem behavior from ages 2 to 4 predicted positive change in caregiver-rated social support and relationship satisfaction over a 3-year period. This indirect effects model is discussed with respect to implications for early childhood prevention research focused on improving family functioning.

Optimizing Educational Video Through Comparative Trials In Clinical Environments. Aronson ID, Plass JL, Bania TC. Educ Technol Res Dev. 2013; 60(3): 469-482.
Although video is increasingly used in public health education, studies generally do not implement randomized trials of multiple video segments in clinical environments. Therefore, the specific configurations of educational videos that will have the greatest impact on outcome measures ranging from increased knowledge of important public health issues, to acceptance of a voluntary HIV test, remain largely unknown. Interventions can be developed to run on affordable handheld computers, including inexpensive tablets or netbooks that each patient can use individually, and to integrate video delivery with automated data collection. These video interventions can then be used not only to educate patients who otherwise might not be reached, but to examine how content can be optimized for greater effectiveness as measured by cognitive and behavioral outcomes. This approach may prove especially valuable in high volume urban facilities, such as hospital emergency departments, that provide points of contact for lower income, lower literacy, and high-risk populations who may not otherwise interact with healthcare providers or researchers. This article describes the development and evaluation

of an intervention that educates emergency department patients about HIV prevention and testing while comparatively examining a set of videos, each based upon competing educational theories. The computer-based video intervention and methodology are both highly replicable and can be applied to subject areas and settings far beyond HIV or the emergency department.

Early School Engagement and Late Elementary Outcomes for Maltreated Children in Foster Care. Pears K, Kim H, Fisher P, Yoerger K, Yoerger K. Dev Psychol. 2013 March 11: Epub ahead of print.

Children with a history of maltreatment and placement into foster care face elevated risks of poor psychosocial outcomes including school failure, substance use, externalizing, and deviant peer association. For children in the general population, school engagement appears to be a promotive factor in preventing negative outcomes. In this study, differences in 3 dimensions of school engagement (behavioral, affective, and cognitive) in early elementary school were explored in maltreated children in foster care (n = 93) and a community comparison group of low-socioeconomic status, nonmaltreated children (n = 54). It was also hypothesized that these 3 dimensions of school engagement would mediate the association between being maltreated and in foster care and several outcomes in late elementary school (Grades 3-5): academic competence, endorsement of substance use, externalizing behaviors, and deviant peer association. Measures were multimethod and multi-informant. Results showed that the children in foster care had lower affective and cognitive school engagement than children in the community comparison group. Structural equation modeling revealed that both affective and cognitive school engagement mediated the association between group status and academic competence in late elementary school. Cognitive engagement also mediated the association between group status and engagement in risk behaviors. The identification of dimensions of early school engagement that predict later outcomes suggests potential points of intervention to change trajectories of academic and behavioral adjustment for maltreated children in foster care.

Measuring Collective Efficacy Among Children in Community-based Afterschool Programs: Exploring Pathways toward Prevention and Positive Youth Development. Smith E, Osgood D, Caldwell L, Hynes K, Perkins D. Am J Community Psychol. 2013 Sep; 52(1-2): 27-40.

Collective efficacy refers to a perceived sense of connectedness and willingness to intervene among youth, and is a potential aspect of positive youth development (Larson in Am Psychol 55: 170-183, 2000; Lerner et al. in Child Dev 71: 11-20, 2000; Sampson et al. in Science 277: 918-924, 1997). Theoretically, those who feel connected to a group that is empowered to positively influence the behavior of their peers may demonstrate fewer problem behaviors. Few studies, however, have measured the impact of youth perceptions of collective efficacy. As a relatively new child-related research topic, there is much to be learned. One contribution to the foundation of this research agenda begins by evaluating the reliability and validity of a measure of collective efficacy with elementary children attending community-based afterschool programs. This paper describes the internal consistency reliability and various indicators of construct and concurrent validity of the Collective Efficacy Among Children Scale. The measure was found to have high internal consistency reliability. Construct validity was tested using exploratory factor analyses of collective efficacy including the dimensions of willingness to intervene and cohesion found in previous research (Sampson et al. in Science

277:918-924, 1997). Concurrent validity assessed relations between the scale and other measures in theoretically congruent ways. Using Hierarchical Linear Models to account for children's nestedness in after-school programs, connectedness was found to be more related to emotional adjustment, particularly children's prosocial attitudes (caring about others and sharing). Children's perception of the willingness of the group to intervene was found to be related to less problem behavior, (i.e. smoking tobacco, drinking alcohol, vandalism, and stealing). The implications suggest that future research should further explore children's collective efficacy, and ways to foster its development in youth-serving afterschool settings.

Random Assignment of Schools to Groups in the Drug Resistance Strategies Rural Project: Some New Methodological Twists. Graham J, Pettigrew J, Miller-Day M, Krieger J, Zhou J, Hecht M. Prev Sci. 2013 May 31: Epub ahead of print.
Random assignment to groups is the foundation for scientifically rigorous clinical trials. But assignment is challenging in group randomized trials when only a few units (schools) are assigned to each condition. In the DRSR project, the authors assigned 39 rural Pennsylvania and Ohio schools to three conditions (rural, classic, control). But even with 13 schools per condition, achieving pretest equivalence on important variables is not guaranteed. The authors collected data on six important school-level variables: rurality, number of grades in the school, enrollment per grade, percent white, percent receiving free/assisted lunch, and test scores. Key to their procedure was the inclusion of school-level drug use data, available for a subset of the schools. Also, key was that the authors handled the partial data with modern missing data techniques. They chose to create one composite stratifying variable based on the seven school-level variables available. Principal components analysis with the seven variables yielded two factors, which were averaged to form the composite inflate-suppress (CIS) score which was the basis of stratification. The CIS score was broken into three strata within each state; schools were assigned at random to the three program conditions from within each stratum, within each state. Results showed that program group membership was unrelated to the CIS score, the two factors making up the CIS score, and the seven items making up the factors. Program group membership was not significantly related to pretest measures of drug use (alcohol, cigarettes, marijuana, chewing tobacco; smallest $p>.15$), thus verifying that pretest equivalence was achieved.

Context Matters: The Moderating Role of Bar Context in the Association Between Substance Use During Sex and Condom Use Among Male Clients of Female Sex Workers in Tijuana, Mexico. Pitpitan E, Wagner K, Goodman-Meza D, Semple S, Chavarin C, Strathdee S, Patterson T. AIDS Behav. 2013; Epub.
Tijuana is situated on Mexico's northern border with the U.S., where sex work is quasi-legal. Whereas previous work has focused on the risk behaviors of female sex workers (FSWs), less is known about the risk behaviors of their male clients. Further, research has not examined structural factors as moderators of the association between substance use and condom use, including the contexts in which sex takes place. The purpose of the current study is to examine whether having sex with FSWs in a bar moderates the link between alcohol intoxication during sex and condom use. The authors recruited 375 male clients of FSWs in Tijuana, Mexico from San Diego, California and Tijuana. Using computer assisted interviewing the authors surveyed participants on their alcohol use, condom use, and physical contexts of sex with FSWs in the past 4 months. Results showed that more frequent intoxication during sex with FSWs is

associated with more unprotected sex, but only among clients having sex with FSWs in a bar context. Results point to potential reasons for inconsistent condom use with FSWs in this context, including lower risk perceptions of sex with FSWs in bars. Future research should examine structural factors that underlie clients; risk behavior in bars in order to inform structural-level HIV prevention interventions.

Treatment-Enhanced Paired Action Contributes Substantially To Change Across Multiple Health Behaviors: Secondary Analyses Of Five Randomized Trials. Yin H, Prochaska J, Rossi J, Redding C, Paiva A, Blissmer B, Velicer W, Johnson S, Kobayashi H. Transl Behav Med. 2013; 3(1): 62-71.
The dominant paradigm of changing multiple health behaviors (MHBs) is based on treating, assessing, and studying each behavior separately. This study focused on individuals with co-occurring baseline health-risk behavior pairs and described whether they changed over time on both or only one of the behaviors within each pair. Data from five randomized trials of computer-tailored interventions (CTIs) that simultaneously treated MHBs were analyzed. The differences between treatment and control proportions that achieved paired action and singular action at 24 months follow-up, and the proportional contribution of paired action to overall change on each behavior, were assessed across 12 behavior pairs (including energy balance, addictive, and appearance-related behaviors). CTIs consistently produced more paired action across behavior pairs. Paired action contributed substantially more to the treatment-related outcomes than singular action. Studying concurrent changes on MHBs as demonstrated allows the effect of simultaneously treating MHBs to be assessed.

Developing the Ho'ouna Pono Substance Use Prevention Curriculum: Collaborating with Hawaiian Youth and Communities. Helm S, Okamoto S. Hawaii J Med Public Health. 2013; 72(2): 66-69.
This article briefly outlines a collaboration among communities on Hawaii Island and a university-based research team to develop, implement, and evaluate a school-based substance use prevention curriculum called Ho'ouna Pono. In addition to providing a rationale for the project, the goal of this paper is fourfold. First, an overview of the Ho'ouna Pono research results to date (2007-2013) is provided. Second, within this overview, the ways in which selected results informed program development are highlighted. Third, the curriculum is briefly described, and finally, the role of the students and community in the video production is described.

Concurrent Choice For Social Interaction and Amphetamine Using Conditioned Place Preference In Rats: Effects Of Age And Housing Condition. Yates J, Beckmann J, Meyer A, Bardo M. Drug Alcohol Depend. 2013; 129(3): 240-246.
Social interaction can serve as a natural reward that attenuates drug reward in rats; however, it is unknown if age or housing conditions alter the choice between social interaction and drug. Individually- and pair-housed adolescent and adult male rats were tested using conditioned place preference (CPP) in separate experiments in which: (1) social interaction was conditioned against no social interaction; (2) amphetamine (AMPH; 1mg/kg, s.c.) was conditioned against saline; or (3) social interaction was conditioned against AMPH. Social interaction CPP was obtained only in individually-housed adolescents, whereas AMPH CPP was obtained in both individually-housed adolescents and adults; however, the effect of

AMPH was not statistically significant in pair-housed adults. When allowed to choose concurrently between compartments paired with either social interaction or AMPH, individually-housed adolescents preferred the compartment paired with social interaction, whereas pair-housed adolescents preferred the compartment paired with AMPH. Regardless of housing condition, adults showed a similar preference for the compartments paired with either social interaction or AMPH. Although some caution is needed in interpreting cross-experiment comparisons, the overall results suggest that individually-housed adolescents were most sensitive to the rewarding effect of social interaction, and this hypersensitivity to social reward effectively competed with AMPH reward.

Differences In HIV Risk Behavior Of Injection Drug Users In New York City By Health Care Setting. Turner AK, Harripersuad K, Crawford ND, Rivera AV, Fuller CM. AIDS Care. 2013; Epub.

The purpose of this study is to examine the HIV risk behaviors and demographic characteristics of injection drug users (IDUs) by type of health care setting, which can inform development of tailored structural interventions to increase access to HIV prevention and medical treatment services. IDU syringe customers were recruited from pharmacies as part of the "Pharmacist As Resources Making Links to Community Services" (PHARM-Link) study, a randomized community-based intervention in New York City (NYC) aimed at connecting IDUs to HIV prevention, medical, and social services. An ACASI survey ascertained demographics, risk behavior, health-care utilization, and location where health care services were received in the past year. Data were analyzed using logistic regression. Of 602 participants, 34% reported receiving health care at a community clinic, 46% a private medical office, 15% a mobile medical unit, and 59% an emergency room (ER). After adjustment, participants who attended a community clinic were significantly more likely to have health insurance, report syringe sharing, and be HIV positive. Whites, nondaily injectors, insured, and higher income IDUs were more likely to attend a private medical office. Participants who recently used a case manager and had multiple sexual partners were more likely to use a mobile medical unit. ER attendees were more likely to be homeless and report recent drug treatment use. These findings show that IDU demographics and risk behaviors differ by health care setting, suggesting that risk reduction interventions should be tailored to health care settings. Specifically, these data suggest that community clinics and mobile medical units serve high-risk IDUs, highlighting the need for more research to develop and test innovative prevention and care programs within these settings.

Intervening with Practitioners to Improve the Quality of Prevention: One-Year Findings from a Randomized Trial of Assets-Getting To Outcomes. Chinman M, Acosta J, Ebener P, Burkhart Q, Malone PS, Paddock SM, Clifford M, Corsello M, Duffey T, Hunter S, Jones M, Lahti M, Phillips A, Savell S, Scales PC, Tellett-Royce N. J Prim Prev. 2013.

There continues to be a gap in prevention outcomes achieved in research trials versus those achieved in "real-world" practice. This article reports interim findings from a randomized controlled trial evaluating Assets-Getting To Outcomes (AGTO), a two-year intervention designed to build prevention practitioners' capacity to implement positive youth development-oriented practices in 12 community coalitions in Maine. A survey of coalition members was used to assess change on individual practitioners' prevention capacity between baseline and one year later. Structured interviews with 32 program directors (16 in the intervention group

and 16 in the control group) were used to assess changes in programs prevention practices during the same time period. Change in prevention capacity over time did not differ significantly between the intervention and control groups. However, in secondary analyses of only those assigned to the AGTO intervention, users showed greater improvement in their self-efficacy to conduct Assets-based programming and increases in the frequency with which they engaged in AGTO behaviors, whereas among non-users, self-efficacy to conduct Assets-based programming declined. Interview ratings showed improvement in several key areas of performance among intervention programs. Improvement was associated with the number of technical assistance hours received. These results suggest that, after one year, AGTO is beginning to improve the capacity of community practitioners who make use of it.

Randomized Trial Of Web-Based Training To Promote Counselor Use Of Cognitive Behavioral Therapy Skills In Client Sessions. Larson MJ, Amodeo M, Locastro JS, Muroff J, Smith L, Gerstenberger E. Subst Abus. 2013; 34(2): 179-187.
The authors designed and delivered an innovative Web course on cognitive behavioral therapy (CBT), a specific empirically based treatment, to a diverse group of addiction counselors and supervisors in 54 addiction units across the country, and conducted a randomized controlled trial of its effectiveness with 127 counselors. The primary focus of the trial was to assess "adequate adherence to CBT practice" after training as judged by raters blinded to training condition who listened to audiotapes of actual client sessions. Counselors who passed were judged to satisfy 2 criteria: (a) low pass or greater on at least 1 of 3 "CBT-generic skills" assessing session structure; and (b) low pass or greater on at least 1 of 3 "CBT-specific skills" related to use of functional analysis, cognitive skills practice, or behavioral skills practice. Although the counselors' use of CBT skills in sessions increased after Web course training, it was not statistically significant and not larger than the gain of control-group counselors trained with a written CBT manual.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Forced Smoking Abstinence: Not Enough for Smoking Cessation. Clarke JG, Stein LA, Martin RA, Martin SA, Parker D, Lopes CE, McGovern AR, Simon R, Roberts M, Friedman P, Bock B. JAMA Intern Med. 2013 May 13; 173(9): 789-794.
Millions of Americans are forced to quit smoking as they enter tobacco-free prisons and jails, but most return to smoking within days of release. Interventions are needed to sustain tobacco abstinence after release from incarceration. The objective of this study was to evaluate the extent to which the WISE intervention (Working Inside for Smoking Elimination), based on motivational interviewing (MI) and cognitive behavioral therapy (CBT), decreases relapse to smoking after release from a smoke-free prison. Participants were recruited approximately 8 weeks prior to their release from a smoke-free prison and randomized to 6 weekly sessions of either education videos (control) or the WISE intervention. The study setting was a tobacco-free prison in the United States. A total of 262 inmates (35% female) served as participants. Continued smoking abstinence was defined as 7-day point-prevalence abstinence validated by urine cotinine measurement. At the 3-week follow-up, 25% of participants in the WISE intervention (31 of 122) and 7% of the control participants (9 of 125) continued to be tobacco abstinent (odds ratio [OR], 4.4; 95% CI, 2.0-9.7). In addition to the intervention, Hispanic ethnicity, a plan to remain abstinent, and being incarcerated for more than 6 months were all associated with increased likelihood of remaining abstinent. In the logistic regression analysis, participants randomized to the WISE intervention were 6.6 times more likely to remain tobacco abstinent at the 3-week follow up than those randomized to the control condition (95% CI, 2.5-17.0). Nonsmokers at the 3-week follow-up had an additional follow-up 3 months after release, and overall 12% of the participants in the WISE intervention (14 of 122) and 2% of the control participants (3 of 125) were tobacco free at 3 months, as confirmed by urine cotinine measurement (OR, 5.3; 95% CI, 1.4-23.8). The authors conclude that forced tobacco abstinence alone during incarceration has little impact on post-release smoking status. A behavioral intervention provided prior to release greatly improves cotinine-confirmed smoking cessation in the community.

Consumers' Experiences in Dual Focus Mutual Aid for Co-occurring Substance Use and Mental Health Disorders. Matusow H, Guarino H, Rosenblum A, Vogel H, Uttaro T, Khabir S, Rini M, Moore T, Magura S. Subst Abuse. 2013; 7: 39-47.
Mutual aid fellowships have been shown to improve outcomes for those with co-occurring substance use and mental illness disorders. Processes associated with usefulness include helper therapy (the assumption of a helping role to foster commitment) and reciprocal learning (the sharing of problems and solutions among members). The present qualitative investigation used focus groups comprised of a subset of participants in Double Trouble in Recovery (DTR), a 12-step mutual aid group for those with co-occurring disorders, to gather their subjective perceptions of the groups. Participants emphasized that in linking them to others with similar problems, the DTR groups played a vital emotional role in their lives and provided a needed venue for information sharing that might have been otherwise unavailable.

Predictors of Lapse in First Week of Smoking Abstinence in PTSD and Non-PTSD Smokers. Beckham JC, Calhoun PS, Dennis MF, Wilson SM, Dedert EA. Nicotine Tob Res. 2013 Jun;15(6): 1122-1129.

Retrospective research suggests smokers with posttraumatic stress disorder (PTSD) lapse more quickly after their quit date. Ecological momentary assessment (EMA) research is needed to confirm the presence of early smoking lapse in PTSD and form conceptualizations that inform intervention. Smokers with (n = 55) and without (n = 52) PTSD completed alarm-prompted EMA of situational and psychiatric variables the week before and after a quit date, and self-initiated EMA following smoking lapses. Blood samples at baseline and on the quit date allowed assessment of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA(S)). Results indicated that PTSD was related to shorter time to lapse (hazard ratio [HR] = 1.677, 95% CI: 1.106-2.544). Increased smoking abstinence self-efficacy was related to longer time to lapse (HR = 0.608, 95% CI: 0.430-0.860). Analyses of participants' real-time reports revealed that smokers with PTSD were more likely to attribute first-time lapses to negative affect (= 5.412, p = .020), and trauma reminders (Fisher's exact p = .003**). Finally, the quit date decrease in DHEA(S) was related to shorter time to lapse (HR = 1.009, 95% CI: 1.000-1.018, p < .05). Results provide evidence of shorter time to first smoking lapse in PTSD, and add to evidence that early lapse occasions are more strongly related to trauma reminders, negative affect, and cravings in smokers with PTSD.

Mobile Contingency Management as an Adjunctive Smoking Cessation Treatment for Smokers With Posttraumatic Stress Disorder. Hertzberg JS, Carpenter VL, Kirby AC, Calhoun PS, Moore SD, Dennis MF, Dennis PA, Dedert EA, Beckham JC. Nicotine Tob Res. 2013 May 3. [Epub ahead of print].

Smokers with posttraumatic stress disorder (PTSD) smoke at higher prevalence rates and are more likely to relapse early in a quit attempt. Innovative methods are needed to enhance quit rates, particularly in the early quit period. Web-based contingency-management (CM) approaches have been found helpful in reducing smoking among other difficult-to-treat smoker populations but are limited by the need for computers. This pilot study builds on the web-based CM approach by evaluating a smartphone-based application for CM named mobile CM (mCM). Following a 2-week training period, 22 smokers with PTSD were randomized to a 4-week mCM condition or a yoked (i.e., noncontingent 4-week mCM condition). All smokers received 2 smoking cessation counseling sessions, nicotine replacement, and bupropion. Participants could earn up to $690 ($530 for mCM, $25.00 for assessments and office visits [up to 5], and $35.00 for equipment return). The average earned was $314.00. Compliance was high during the 2-week training period (i.e., transmission of videos) (93%) and the 4-week treatment period (92%). Compliance rates did not differ by group assignment. Four-week quit rates (verified with CO) were 82% for the mCM and 45% for the yoked controls. Three-month self-report quit rates were 50% in the mCM and 18% in the yoked controls. The authors conclude that mCM may be a useful adjunctive smoking cessation treatment component for reducing smoking among smokers with PTSD, particularly early in a smoking quit attempt.

The Effect of Framing Incentives as Either Losses or Gains with Contingency Management for Smoking Cessation. Romanowich P, Lamb RJ. Addict Behav. 2013 Apr; 38(4): 2084-2088.
Cumulative prospect theory predicts that losses motivate behavior more than equal gains. Contingency management procedures effectively reduce drug use by placing incentives in direct competition with the drug taking behavior. Therefore, framing incentives as losses, rather than gains should decrease drug use to a greater extent, given equivalent incentives. The authors examined whether contingent vouchers described as either losses or gains differentially affected smoking abstinence rates. Over 5 consecutive days, participants could either gain $75 per day for verified abstinence or lose $75 per day (initial endowment=$375) for continuing to smoke. As a result, loss-framed participants were more likely to achieve at least one day of abstinence. There was a trend towards loss-framed participants reducing the amount smoked more than gain-framed participants. However, participants in the gain-framed group were more likely to maintain abstinence, once initiated. The results partially support cumulative prospect theory and suggest additional ways to initiate behavior change using incentives, outside of using larger magnitude incentives in contingency management procedures.

Illicit Drug Use among Pregnant Women Enrolled in Treatment for Cigarette Smoking Cessation. Gaalema DE, Higgins ST, Pepin CS, Heil SH, Bernstein IM. Nicotine Tob Res. 2013 May;15(5): 987-991.
Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes in the United States. In population studies and nationwide surveys, pregnant smokers report more illicit drug use than pregnant nonsmokers. The purpose of this study was to examine the prevalence of illicit drug use among pregnant women enrolled in clinical trials for smoking cessation. Urine specimens from 115 pregnant women were tested for illicit drug use during a study intake visit (~10th week of pregnancy) and during the final antepartum (FAP) smoking-status assessment (~28th week of pregnancy). Participants smoked about 18 cigarettes/day prepregnancy, were generally young (<25 years), Caucasian, with a high school education and without private insurance. About 34% of specimens from the intake visit and 25% of those from the FAP assessment tested positive for an illicit drug. The most common drug detected was marijuana (90% of positive specimens), followed by opioids (18%), cocaine (5%), benzodiazepines (3%), and methadone (3%). None tested positive for amphetamines. The majority of women (53%) who tested positive for an illicit substance at intake also tested positive at the FAP assessment. Approximately a quarter to a third of pregnant women enrolled in these smoking-cessation trials were determined to be using illicit drugs, with marijuana use being the most prevalent. Those providing smoking-cessation services to pregnant women may want to be prepared to assist with obtaining services for other drug use as well.

Characteristics of Cigarette Smokers Who Want to Quit Now versus Quit Later. Burris JL, Wahlquist AE, Carpenter MJ. Addict Behav. 2013 Jun; 38(6): 2257-2260.
This study evaluated factors associated with adult smokers' immediate readiness to quit. Eligible smokers were proactively recruited online and invited to participate in either a telephone-based study for those who intend to quit in the next 30days (Quit Now) or a telephone-based study for those who intend to quit, but not in the next month (Quit Later).

Thirty-five percent of smokers declined participation altogether. Of those who remained, 25% chose Quit Now participation. Baseline data were collected via mail questionnaire and telephone interview. Quit Now and Quit Later participants (N=1132) differed on demographic, smoking history, and psychological variables. Independent predictors of Quit Now group membership included younger age, stronger intention to quit in the next six months, greater self-efficacy to cope with temptation to smoke, and more support from significant others related to quit attempts-much of which is modifiable. Understanding factors that predict smokers' immediate readiness to quit (measured here as Quit Now group membership) could contribute to the development of smoking cessation treatments tailored for smokers who are seemingly not yet ready to quit.

Predictors of Quit Attempts and Successful Quit Attempts in a Nationally Representative Sample of Smokers. Rafful C, García-Rodríguez O, Wang S, Secades-Villa R, Martínez-Ortega JM, Blanco C. Addict Behav. 2013 Apr; 38(4): 1920-1923.
Although most current smokers report that they would like to quit, most quit attempts fail suggesting that predictors of quitting attempts may differ from those of successful attempts. The authors examined sociodemographic and clinical predictors of quit attempts and successful quit attempts in a nationally representative sample of US adults. Data was collected in 2001-2002 (Wave 1) and 2004-2005 (Wave 2). Almost 40% of individuals who had not previously attempted to quit, tried to quit over the next three years; only 4.6% of those who tried had succeeded at the time of the evaluation. Hispanics, Asians, individuals with high income, and those with college education were less likely to attempt to quit, whereas those with daily nicotine use, younger age at first use and most symptoms of dependence were more likely to do so. Having an educational level below high school and older age at first nicotine use were predictors of successful quitting. Despite relatively high rates of quit attempts, rates of success are extremely low, indicating a gap between the public health need of decreasing tobacco use, and existing means to achieve it. Although there is a need to encourage people to quit tobacco, there may be an equally large need to develop more effective interventions that increase the rate of successful quit attempts.

Cognitive Function during Nicotine Withdrawal: Implications for Nicotine Dependence Treatment. Ashare RL, Falcone M, Lerman C. Neuropharmacology. 2013 Apr 29. pii: S0028-3908(13)00180-9.
Nicotine withdrawal is associated with deficits in neurocognitive function including sustained attention, working memory, and response inhibition. Several convergent lines of evidence suggest that these deficits may represent a core dependence phenotype and a target for treatment development efforts. A better understanding of the mechanisms underlying withdrawal-related cognitive deficits may lead to improved nicotine dependence treatment. The authors begin with an overview of the neurocognitive effects of withdrawal in rodent and human models, followed by discussion of the neurobehavioral mechanisms that are thought to underlie these effects. They then review individual differences in withdrawal-related neurocognitive effects including genetics, gender, and psychiatric comorbidity. They conclude with a discussion of the implications of this research for developing improved therapies, both pharmacotherapy and behavioral treatments, that target cognitive symptoms of nicotine withdrawal.

User Preferences for a Text Message-based Smoking Cessation Intervention. Bock BC, Heron KE, Jennings EG, Magee JC, Morrow KM. Health Educ Behav. 2013 Apr; 40(2): 152-159.
Younger adults are more likely to smoke and less likely to seek treatment than older smokers. They are also frequent users of communication technology. In the current study, the authors conducted focus groups to obtain feedback about preferences for a text message-based smoking cessation program from potential users. Participants (N = 21, M age = 25.6 years, age range = 20-33 years) were current or recently quit smokers (M cigarettes/day = 12.8) who used text messaging. Participants completed questionnaires and participated in a 2-hour focus group. Focus groups were conducted using an a priori semistructured interview guide to promote discussion of the content and functionality of the intervention. Major themes from analysis of the focus groups included support for the acceptability of a text-based cessation program, suggestions for a more technologically broad-based program, and adjustments to the program structure. Participants recommended including social networking functions, user control of program output through an online profile, and text message features to promote interaction with the system. Interestingly, many participants suggested the program should begin on individuals' identified quit day, challenging the procedures used in most cessation programs, which begin by preparing participants for a future quit date. Overall, younger adult smokers appear to be interested in participating in a smoking cessation program that uses text messages and web-based elements. Qualitative feedback regarding the perceived optimal features and structure of a technology-based intervention challenged traditional methods of implementing smoking cessation interventions and will inform the development of future programs.

A Preliminary Experimental Investigation of Peer Influence on Risk-taking among Adolescent Smokers and Non-smokers. Cavalca E, Kong G, Liss T, Reynolds EK, Schepis TS, Lejuez CW, Krishnan-Sarin S. Drug Alcohol Depend. 2013 Apr 1; 129(1-2): 163-166.
Epidemiological evidence suggests that peer influence plays a significant role in a variety of adolescent risk-taking behaviors, including tobacco use. The authors attempted to establish this relationship in a controlled laboratory setting. They modified the Balloon Analog Risk Task (BART) task to include a peer component to investigate whether peer influences alter risk-taking behaviors. Thirty-nine adolescents (22 smokers, 17 non-smokers) completed one experimental session during which the standard and peer BART were presented in counterbalanced order, with the dependent measures being adjusted mean number of pumps and explosions. The authors also examined the relationship of changes in the BART (standard-peer) to personality measures of impulsivity (BIS-11) and resistance to peer influence (RPI). A significant interaction of BART type and smoking status was present (p=.05); specifically smokers had a greater increase in the number of explosions by 2.27 (SD=3.12) compared to an increase of .29 (SD=2.87) by non-smokers. BIS-11 scores were related to peer-influenced BART changes: those who were more impulsive experienced greater changes in risk-taking, but no similar relationships were observed for the RPI. These results suggest that peer influences enhance risk-taking among adolescents, and that smokers may be more susceptible to these influences.

Preventing Addiction Related Suicide: a Pilot Study. Voss WD, Kaufman E, O'Connor SS, Comtois KA, Conner KR, Ries RK. J Subst Abuse Treat. 2013 May-Jun;44(5): 565-569. Persons addicted to alcohol and drugs are at 5-10 times higher risk for suicide as compared to the general population. To address the need for improved suicide prevention strategies in this population, the Preventing Addiction Related Suicide (PARS) module was developed. Pilot testing of 78 patients demonstrated significant post-treatment changes in knowledge [$t(66) = 12.07$, $p = .000$] and attitudes [$t(75) = 6.82$, $p = .000$] toward suicide prevention issues. Significant gains were maintained at 1-month follow-up for changes in knowledge [$t(55) = 6.33$, $p = .000$] and attitudes [$t(61) = 3.37$, $p = .0001$], with changes in positive help seeking behaviors in dealing with suicidal issues in friends [$\chi(2)(1) = 10.49$, $p = .007$], family [$\chi(2)(1) = 9.81$, $p = .015$], and self [$\chi(2)(1) = 19.62$, $p = .008$] also observed. The PARS was also highly rated by treatment staff as feasible within their standard clinical practice.

Smoking-related Weight Concerns and Obesity: Differences among Normal Weight, Overweight, and Obese Smokers using a Telephone Tobacco Quitline. Levine MD, Bush T, Magnusson B, Cheng Y, Chen X. Nicotine Tob Res. 2013 Jun; 15(6): 1136-1140. Substantial evidence suggests that concerns about postcessation weight gain interfere with cessation efforts. However, it is unclear to what extent weight pretreatment affects smoking-related weight concerns. Given that the prevalence of overweight and obesity among callers to tobacco quitlines mirrors that of the population at large, and that women and obese smokers may be more concerned about weight gain, the authors sought to compare weight gain concerns among normal weight, overweight, and obese callers to a quitline. A sample of 34.6% ($n = 206$) normal weight, 30.6% ($n = 182$) overweight, and 34.8% ($n = 207$) obese quitline callers completed assessments of tobacco use history and smoking-specific weight concerns. Weight categories were compared and gender differences evaluated. Obese smokers endorsed significantly more concerns about postcessation weight gain [$F(2, 592) = 20.35$, $p < .0001$], had less confidence in their ability to maintain their weight without smoking [$F(2, 592) = 7.67$, $p = .0005$], and were willing to tolerate less weight gain after quitting than normal weight or overweight smokers [$F(2,574) = 30.59$, $p < .0001$). There also were gender differences in weight concerns by weight status. Significantly more women callers were obese (38.2% vs. 28.4%, $p = .011$), and women consistently endorsed more concern about postcessation weight gain than did men [$F(1,588) = 24.04$, $p < .0001$). The authors conclude that overweight and obese smokers, particularly women, express substantial concern about gaining weight after quitting. It is possible that smokers who begin quitline treatment with a BMI in the obese range may benefit from adjunctive interventions designed to address smoking-related weight concerns.

Investigating Group Contingencies to Promote Brief Abstinence from Cigarette Smoking. Meredith SE, Dallery J. Exp Clin Psychopharmacol. 2013 Apr; 21(2): 144-154. In contingency management (CM), monetary incentives are contingent on evidence of drug abstinence. Typically, incentives (e.g., "vouchers" exchangeable for goods or services) are contingent on individual performance. The authors programmed vouchers contingent on group performance to investigate whether these contingencies would promote brief abstinence from cigarette smoking. Thirty-two participants were divided into small teams ($n = 3$ per team). During three 5-day within-subject experimental conditions, participants submitted video recordings of breath carbon monoxide (CO) measures twice daily via Motiv8 Systems, an

Internet-based remote monitoring application. During the interdependent contingency condition, participants earned vouchers each time they and their teammates submitted breath CO samples indicative of abstinence (i.e., negative samples). During the independent contingency condition, participants earned vouchers each time they submitted negative samples, regardless of their teammates' performance. During the no vouchers condition, no monetary incentives were contingent on abstinence. In addition, half of the participants (n = 16) could communicate with their teammates through an online peer support forum. Although forum access did not appear to promote smoking abstinence, monetary incentives did promote brief abstinence. Significantly more negative samples were submitted when vouchers were contingent on individual performance (56%) or team performance (53%) relative to when no vouchers were available (35%; $F = 6.9$, $p = .002$). The results show that interdependent contingencies can promote brief abstinence from cigarette smoking. Moreover, the results suggest that these contingencies may help lower treatment costs and promote social support.

An Exploratory Randomized Controlled Trial of a Novel High-School-Based Smoking Cessation Intervention for Adolescent Smokers using Abstinence-Contingent Incentives and Cognitive Behavioral Therapy. Krishnan-Sarin S, Cavallo DA, Cooney JL, Schepis TS, Kong G, Liss TB, Liss AK, McMahon TJ, Nich C, Babuscio T, Rounsaville BJ, Carroll KM. Drug Alcohol Depend. 2013 Mar 21. pii: S0376-8716(13)00094-X.
There are few effective smoking cessation interventions for adolescent smokers. The authors developed a novel intervention to motivate tobacco use behavior change by (1) enhancing desire to quit through the use of abstinence-contingent incentives (CM), (2) increasing cessation skills through the use of cognitive behavioral therapy (CBT), and (3) removing cessation barriers through delivery within high schools. An exploratory four-week, randomized controlled trial was conducted in Connecticut high schools to dismantle the independent and combined effects of CM and CBT; smokers received CM alone, CBT alone, or CM+CBT. Participants included 82 adolescent smokers seeking smoking cessation treatment. The primary outcome was seven-day end-of-treatment (EOT) point prevalence (PP) abstinence, determined using self-reports confirmed using urine cotinine levels. Secondary outcomes included one-day EOT PP abstinence and cigarette use during treatment and follow up. Among participants who initiated treatment (n=72), group differences in seven-day EOT-PP abstinence were observed (X^2=10.48, p<0.01) with higher abstinence in the CM+CBT (36.7%) and CM (36.3%) conditions when compared with CBT (0%). One-day EOT-PP abstinence evidenced similar effects (X^2=10.39, p<0.01; CM+CBT: 43%, CM: 43%, CBT: 4.3%). Survival analyses indicated differences in time to first cigarette during treatment (X^2=8.73, p=0.003; CBT: Day 3, CM: Day 9, CM+CBT: Day 20). At one- and three-month follow ups, while no differences were observed, the CM alone group had the slowest increase in cigarette use. The authors conclude that high-school, incentive-based smoking cessation interventions produce high rates of short-term abstinence among adolescent smokers; adding cognitive behavioral therapy does not appear to further enhance outcomes.

Factors Predicting Smoking in a Laboratory-based Smoking-Choice Task. Bold KW, Yoon H, Chapman GB, McCarthy DE. Exp Clin Psychopharmacol. 2013 Apr; 21(2):133-143.
This study aimed to expand the current understanding of smoking maintenance mechanisms by examining how putative relapse risk factors relate to a single behavioral smoking choice using a novel laboratory smoking-choice task. After 12 hr of nicotine deprivation, participants were

exposed to smoking cues and given the choice between smoking up to two cigarettes in a 15-min window or waiting and receiving four cigarettes after a delay of 45 min. Greater nicotine dependence, higher impulsivity, and lower distress tolerance were hypothesized to predict earlier and more intensive smoking. Out of 35 participants (n = 9 women), 26 chose to smoke with a median time to a first puff of 1.22 min (SD = 2.62 min, range = 0.03-10.62 min). Survival analyses examined latency to first puff, and results indicated that greater pretask craving and smoking more cigarettes per day were significantly related to smoking sooner in the task. Greater behavioral disinhibition predicted shorter smoking latency in the first 2 min of the task, but not at a delay of more than 2 min. Lower distress tolerance (reporting greater regulation efforts to alleviate distress) was related to more puffs smoked and greater nicotine dependence was related to more time spent smoking in the task. This novel laboratory smoking-choice paradigm may be a useful laboratory analog for the choices smokers make during cessation attempts and may help identify factors that influence smoking lapses.

Dissemination and Implementation of Cognitive Behavioral Therapy for Stimulant Dependence: A Randomized Trial Comparison of 3 Approaches. Rawson RA, Rataemane S, Rataemane L, Ntlhe N, Fox RS, McCuller J, Brecht ML. Subst Abuse. 2013 Apr-Jun; 34(2): 108-117. doi: 10.1080/08897077.2012.691445.

This study evaluated the effectiveness of 3 approaches to transferring cognitive behavioral therapy (CBT) to addiction clinicians in the Republic of South Africa (RSA). Clinicians (N = 143) were assigned to 3 training conditions: (1) an *in vivo* (IV) approach in which clinicians received in-person training and coaching; (2) a distance learning (DL) approach providing training via videoconference and coaching through teleconferencing; and (3) a control condition (C) providing a manual and 2-hour orientation. Frequency of use of CBT skills increased significantly with the IV and DL approaches compared with the C approach, and the IV approach facilitated greater use of CBT skills than the DL approach. During the active phase of the study, skill quality declined significantly for clinicians trained in the C condition, whereas those in the DL approach maintained skill quality and those in the IV approach improved skill quality. After coaching was discontinued, clinicians in the IV and DL approaches declined in skill quality. However, those in the IV approach maintained a higher level of skill quality compared with the other approaches. Cost of the IV condition was double that of the DL condition and 10 times greater than the C condition. The authors conclude that in vivo supervision and distance learning methods appear to be effective dissemination and implementation strategies, and distance learning has significant potential to be less costly.

A Randomized Trial of Cognitive Behavioral Therapy in Primary Care-Based Buprenorphine. Fiellin DA, Barry DT, Sullivan LE, Cutter CJ, Moore BA, O'Connor PG, Schottenfeld RS. Am J Med. 2013 Jan; 126(1): 74.e11-7. doi: 10.1016/ j.amjmed. 2012.07.005.

The objective of this study was to determine the impact of cognitive behavioral therapy on outcomes in primary care, office-based buprenorphine/naloxone treatment of opioid dependence. The authors conducted a 24-week randomized clinical trial in 141 opioid-dependent patients in a primary care clinic. Patients were randomized to physician management or physician management plus cognitive behavioral therapy. Physician management was brief, manual guided, and medically focused; cognitive behavioral therapy was manual guided and provided for the first 12 weeks of treatment. The primary outcome

measures were self-reported frequency of illicit opioid use and the maximum number of consecutive weeks of abstinence from illicit opioids, as documented by urine toxicology and self-report. The 2 treatments had similar effectiveness with respect to reduction in the mean self-reported frequency of opioid use, from 5.3 days per week (95% confidence interval, 5.1-5.5) at baseline to 0.4 (95% confidence interval, 0.1-0.6) for the second half of maintenance (P<.001 for the comparisons of induction and maintenance with baseline), with no differences between the 2 groups (P=.96) or between the treatments over time (P=.44). For the maximum consecutive weeks of opioid abstinence there was a significant main effect of time (P<.001), but the interaction (P=.11) and main effect of group (P=.84) were not significant. No differences were observed on the basis of treatment assignment with respect to cocaine use or study completion. The authors concluded that among patients receiving buprenorphine/naloxone in primary care for opioid dependence, the effectiveness of physician management did not differ significantly from that of physician management plus cognitive behavioral therapy.

Neuroeconomics and Adolescent Substance Abuse: Individual Differences in Neural Networks and Delay Discounting. Stanger C, Elton A, Ryan SR, James GA, Budney AJ, Kilts CD. J Am Acad Child Adolesc Psychiatry. 2013 Jul; 52(7): 747-755.
Many adolescents with substance use problems show poor response to evidence-based treatments. Treatment outcome has been associated with individual differences in impulsive decision making as reflected by delay discounting (DD) rates (preference for immediate rewards). Adolescents with higher rates of DD were expected to show greater neural activation in brain regions mediating impulsive/habitual behavioral choices and less activation in regions mediating reflective/executive behavioral choices. Thirty adolescents being treated for substance abuse completed a DD task optimized to balance choices of immediate versus delayed rewards, and a control condition accounted for activation during magnitude valuation. A group independent component analysis on functional magnetic resonance imaging time courses identified neural networks engaged during DD. Network activity was correlated with individual differences in discounting rate. Higher discounting rates were associated with diminished engagement of an executive attention control network involving the dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, inferior parietal cortex, cingulate cortex, and precuneus. Higher discounting rates also were associated with less deactivation in a "bottom-up" reward valuation network involving the amygdala, hippocampus, insula, and ventromedial prefrontal cortex. These 2 networks were significantly negatively correlated. Results support relations between competing executive and reward valuation neural networks and temporal decision making, an important, potentially modifiable risk factor relevant for the prevention and treatment of adolescent substance abuse.

Cognitive Enhancement as a Treatment for Drug Addictions. Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Neuropharmacology. 2013 Jan; 64: 452-463.
Drug addiction continues to be an important public health problem, with an estimated 22.6 million current illicit drug users in the United States alone. For many addictions, including cocaine, methamphetamine, and marijuana addiction, there are no approved pharmacological treatments. Behavioral treatments are effective but effects vary widely across individuals. Treatments that are effective across multiple addictions are greatly needed, and accumulating evidence suggests that one such approach may be pharmacological or behavioral interventions

that enhance executive inhibitory control in addicts. Current evidence indicates that most forms of chronic drug use may be associated with significant cognitive impairments, especially in attention, working memory, and response inhibition functions. In some studies, these impairments predict poor treatment retention and outcome. A number of cognitive enhancing agents, including galantamine, modafinil, atomoxetine, methylphenidate, and guanfacine, have shown promising findings in human studies. Specific behavioral interventions, including cognitive remediation, also show promise. However, whether improvement of selective cognitive functions reduces drug use behavior remains to be determined. Cognitive enhancement to improve treatment outcomes is a novel strategy worthy of future research, as are related questions such as whether these approaches may be broadly beneficial to most addicts or best reserved for substance users with specific demonstrated cognitive impairments.

A Qualitative Analysis of Women's Experiences in Single-Gender Versus Mixed-Gender Substance Abuse Group Therapy. Greenfield SF, Cummings AM, Kuper LE, Wigderson SB, Koro-Ljungberg M. Subst Use Misuse. 2013 Jun; 48(9): 772-782.
The present study of women with substance use disorders used grounded theory to examine women's experiences in both the Women's Recovery Group (WRG) and a mixed-gender Group Drug Counseling (GDC). Semi-structured interviews were completed in 2005 by 28 women in a U.S. metropolitan area. Compared to GDC, women in WRG more frequently endorsed feeling safe, embracing all aspects of one's self, having their needs met, feeling intimacy, empathy, and honesty. In addition, group cohesion and support allowed women to focus on gender-relevant topics supporting their recovery. These advantages of single-gender group therapy can increase treatment satisfaction and improve treatment outcomes.

Twice Stigmatized: Provider's Perspectives on Drug-Using Women in the Republic of Georgia. Kirtadze I, Otiashvili D, O'Grady KE, Zule W, Krupitsky E, Wechsberg WM, Jones HE. J Psychoactive Drugs. 2013 Jan-Mar; 45(1): 1-9.
This study examined attitudes and perspectives of 34 health service providers through in-depth interviews in the Republic of Georgia who encountered an injection drug-using woman at least once in the past two months. Most participants' concept of drug dependence treatment was detoxification, as medication-assisted therapy was considered part of harm reduction, although it was thought to have relatively better treatment outcomes compared to detoxification. Respondents reported that drug dependence in women is much more severe than in men. They also expressed less tolerance towards drug-using women, as most providers view such women as failures as a good mother, wife, or child. Georgian women are twice stigmatized, once by a society that views them as fulfilling only a limited purposeful role and again by their male drug-using counterparts. Further, the vast majority of respondents were unaware of the availability of specific types of drug-treatment services in their city, and even more did not seek connections with other service providers, indicating a lack of linkages between drug-related and other services. The need for women-specific services and a comprehensive network of service linkages for all patients in drug treatment is critical. These public health issues require immediate consideration by policy makers, and swift action to address them.

Randomized Clinical Trial Examining Duration of Voucher-Based Reinforcement Therapy for Cocaine Abstinence. Kirby KC, Carpenedo CM, Dugosh KL, Rosenwasser BJ, Benishek LA, Janik A, Keashen R, Bresani E, Silverman K. Drug Alcohol Depend. 2013 May 13. [Epub ahead of print].

This is the first study to systematically manipulate duration of voucher-based reinforcement therapy (VBRT) to see if extending the duration increases abstinence during and following VBRT. The authors randomized cocaine-dependent methadone-maintained adults to Standard (12 weeks; n=62) or Extended (36 weeks; n=68) VBRT and provided escalating voucher amounts contingent upon urinalysis verification of cocaine abstinence. Urinalysis was scheduled at least every 2 weeks during the 48-week study and more frequently during VBRT (3/week) and 12 weeks of Aftercare (2/week). Extended VBRT produced longer durations of continuous cocaine abstinence during weeks 1-24 (5.7 vs 2.7 weeks; p=0.003) and proportionally more abstinence during weeks 24-36 (X^2=4.57, p=.03, OR=2.18) compared to Standard VBRT. Duration of VBRT did not directly predict after-VBRT abstinence; but longer continuous abstinence during VBRT predicted abstinence during Aftercare (p=0.001) and during the last 12 weeks of the study (p<0.001). Extended VBRT averaged higher monthly voucher costs compared to Standard VBRT ($96 vs $43, p<.001); however, the average cost per week of abstinence attained was higher in the Standard group ($8.06 vs $5.88, p<.001). Participants in the Extended group with voucher costs exceeding $25 monthly averaged 20 weeks of continuous abstinence. Greater abstinence occurred during Extended VBRT, but providing a longer duration was not by itself sufficient to maintain abstinence after VBRT. However, if abstinence can be captured and sustained during VBRT, then providing longer durations may help increase the continuous abstinence that predicts better long-term outcomes.

Rumination Mediates the Relationship between Distress Tolerance and Depressive Symptoms among Substance Users. Magidson JF, Listhaus AR, Seitz-Brown CJ, Anderson KE, Lindberg B, Wilson A, Daughters SB. Cognit Ther Res. 2013 Jun 1; 37(3): 456-465.

Distress tolerance has been implicated in the emergence of internalizing symptomatology, notably depressive symptoms. However, few studies have tested potential mechanisms underlying the relationship between distress tolerance and depressive symptoms, and further, this has not been tested among substance users, who commonly experience both low distress tolerance and elevated depressive symptoms. The current study focused on the construct of rumination, which has been suggested to be a coping response to stress associated with substance use and depression. Two forms of rumination, brooding and reflection, were tested as potential mediators of the relationship between distress tolerance and self-reported depressive symptoms among 128 individuals entering substance abuse treatment. Brooding (i.e., to overly focus on symptoms of distress) mediated the relationship between distress tolerance and depressive symptoms. However, reflection (i.e., to attempt to gain insight into problems) was unrelated to distress tolerance. Findings suggest the important role of brooding as a mechanism underlying the relationship between distress tolerance and depressive symptomatology.

Change in Parent- and Child-Reported Internalizing and Externalizing Behaviors Among Substance Abusing Runaways: The Effects of Family and Individual Treatments.
Slesnick N, Guo X, Feng X. J Youth Adolesc. 2013 Jul; 42(7): 980-993.
Shelter-recruited adolescents are known to have high rates of substance abuse and co-occurring internalizing and externalizing problem behaviors. Many studies have documented these mental health concerns, but only a small number of studies have tested interventions that may be useful for ameliorating these vulnerabilities. The current study compared three empirically supported psychotherapy interventions, Motivational Interviewing (MI), the Community Reinforcement Approach (CRA), and Ecologically-Based Family Therapy (EBFT) with 179 substance abusing runaway adolescents (47 % female, 74 % minority) and their primary caretaker recruited through a Midwestern runaway crisis shelter. Examining both child and primary caretaker reports, each treatment was associated with significant reductions in internalizing and externalizing behaviors to 24 months post-baseline. However, the trajectory of change differed among the treatments. Adolescents receiving MI showed a quicker reduction in internalizing and externalizing behaviors but also a quicker increase in these behaviors compared to adolescents receiving EBFT, who continued to evidence improvements to 24 months. The findings provide support for continued evaluation of these treatments for use with this vulnerable population of adolescents.

Parenting of Men with Co-Occurring Intimate Partner Violence and Substance Abuse Source. Stover CS, Easton CJ, McMahon TJ. J Interpers Violence. 2013 Jul; 28(11): 2290-2314.
No studies to date have compared parenting behaviors of men with co-occurring intimate partner violence (IPV) and substance abuse (SA) with community controls. This study was designed to document mediators of differences in parenting behavior of fathers and the emotional-behavioral problems of their children for men with co-occurring SA and IPV. The self-reported parenting (negative, positive and co-parenting behaviors) and the child emotional-behavioral problems of 43 fathers with children aged 2 to 6 years with a recent history of SA + IPV were compared to a sample of 43 community control fathers with the same socioeconomic and cultural backgrounds. Fathers completed measures on their parenting behavior with a target child, co-parenting behavior with the child's mother, emotion regulation, romantic attachment, psychiatric symptoms, and the behavior of the target child. Men with co-occurring SA + IPV had significantly less positive co-parenting and more negative parenting behaviors than community control fathers. Negative parenting and co-parenting were mediated by the fathers' avoidant attachment problems. SA + IPV fathers also reported more emotional and behavioral problems in their children. These poor child outcome differences between groups were mediated by the negative parenting behaviors of the fathers. These results suggest areas of potential focus in interventions with fathers who have co-occurring SA + IPV issues. Focus on attachment difficulties with his co parent, which may include affect regulation, coping with emotions, and communication skills training related to co-parenting, may yield significant changes in parenting behaviors and ultimately child functioning.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Amygdala-Dependent Fear Is Regulated by Oprl1 in Mice and Humans with PTSD. Andero R, Brothers SP, Jovanovic T, Chen YT, Salah-Uddin H, Cameron M, Bannister TD, Almli L, Stevens JS, Bradley B, Binder EB, Wahlestedt C, Ressler KJ. Sci Transl Med. 2013 Jun 5; 5(188):188ra73. doi: 10.1126/scitranslmed.3005656.

The amygdala-dependent molecular mechanisms driving the onset and persistence of posttraumatic stress disorder (PTSD) are poorly understood. Recent observational studies have suggested that opioid analgesia in the aftermath of trauma may decrease the development of PTSD. Using a mouse model of dysregulated fear, the authors found altered expression within the amygdala of the Oprl1 gene (opioid receptor-like 1), which encodes the amygdala nociceptin (NOP)/orphanin FQ receptor (NOP-R). Systemic and central amygdala infusion of SR-8993, a new highly selective NOP-R agonist, impaired fear memory consolidation. In humans, a single-nucleotide polymorphism (SNP) within OPRL1 is associated with a self-reported history of childhood trauma and PTSD symptoms (n = 1847) after a traumatic event. This SNP is also associated with physiological startle measures of fear discrimination and magnetic resonance imaging analysis of amygdala-insula functional connectivity. Together, these data suggest that Oprl1 is associated with amygdala function, fear processing, and PTSD symptoms. Further, these data suggest that activation of the Oprl1/NOP receptor may interfere with fear memory consolidation, with implications for prevention of PTSD after a traumatic event.

Effects Of Methcathinone and 3-Cl-Methcathinone (PAL-434) In Cocaine Discrimination Or Self-Administration In Rhesus Monkeys. Kohut SJ, Fivel PA, Blough BE, Rothman RB, Mello NK. Int J Neuropsychopharmacol. 2013 Jun 17: 1-14. [Epub ahead of print].

Monoamine releasers with varying selectivity for dopamine (DA)/norepinephrine and serotonin (5-HT) release are potential treatment medications for cocaine abuse. Although DA-selective monoamine releasers effectively reduce cocaine abuse, their clinical usefulness is limited by abuse liability. It is hypothesized that increasing 5-HT neurotransmission may reduce the abuse-related effects of DA releasers, but the optimal DA:5-HT release ratio remains to be determined. This study in rhesus monkeys compared the effects of two compounds with differing potency for 5-HT release. Methcathinone and 3-Cl-methcathinone (PAL-434) have equal potency for DA release, but PAL-434 has 10-fold higher potency for 5-HT release. In drug discrimination studies, monkeys were trained to discriminate cocaine (0.4 mg/kg i.m.) from saline in a two-key, food-reinforced procedure. In drug self-administration studies, a separate group of monkeys was trained to respond for cocaine [0.01 mg/kg/injection (inj)] and food (1 g pellets) under a second order schedule of reinforcement [FR2(VR16:S)]. When responding was stable, methcathinone (0.1-0.56 mg/kg.h i.v.) or PAL-434 (0.32-1.8 mg/kg.h i.v.) was administered chronically (one injection every 20 min for 23 h/d) for 7-10 d. In discrimination studies, both compounds dose-dependently increased cocaine-like responding but with different potencies (cocaine=methcathinone >PAL-434). Chronic treatment with methcathinone or PAL-434 dose-dependently and selectively reduced cocaine self-administration. PAL-434 was about 4-fold and methcathinone about 1.6-fold more potent at decreasing cocaine- over food-maintained responding. These data suggest that compounds with moderate selectivity for DA vs. 5-HT release (8-15-fold) may be effective for the treatment of cocaine dependence.

Designing Bifunctional NOP Receptor-Mu Opioid Receptor Ligands From NOP Receptor-Selective Scaffolds. Part I. Zaveri NT, Jiang F, Olsen C, Polgar WE, Toll L. Bioorg Med Chem Lett. 2013 Jun 1; 23(11): 3308-3313. doi: 10.1016/j.bmcl.2013.03.101. Epub 2013 Apr 4.
The nociceptin receptor (NOP) and its endogenous agonist, nociceptin/orphanin FQ (N/OFQ), members of the opioid receptor and peptide families respectively, modulate the pharmacological effects of classical opioids, particularly opioid-induced reward and nociception. The authors hypothesized that compounds containing both NOP and opioid receptor activity in a single molecule may have useful pharmacological profiles as non-addicting analgesics or as drug abuse medications. They report here their forays into the structure-activity relationships for discovering 'bifunctional' NOP-mu opioid receptor (MOP) ligands, starting from our NOP-selective scaffolds. This initial SAR suggests pharmacophoric elements that may be modified to modulate/increase opioid affinity, while maintaining high affinity for the NOP receptor, to result in potent bifunctional small-molecule NOP/MOP ligands.

Pyrrolidine Analogs Of GZ-793A: Synthesis and Evaluation As Inhibitors Of the Vesicular Monoamine Transporter-2 (VMAT2). Penthala NR, Ponugoti PR, Nickell JR, Deaciuc AG, Dwoskin LP, Crooks PA. Bioorg Med Chem Lett. 2013 Jun 1; 23(11): 3342-3345. doi: 10.1016/j.bmcl.2013.03.092. Epub 2013 Apr 2.
Central heterocyclic ring size reduction from piperidinyl to pyrrolidinyl in the vesicular monoamine transporter-2 (VMAT2) inhibitor GZ-793A and its analogs resulted in novel N-propane-1,2(R)-diol analogs 11a-i. These compounds were evaluated for their affinity for the dihydrotetrabenazine (DTBZ) binding site on VMAT2 and for their ability to inhibit vesicular dopamine (DA) uptake. The 4-difluoromethoxyphenethyl analog 11f was the most potent inhibitor of [(3)H]-DTBZ binding (Ki=560 nM), with 15-fold greater affinity for this site than GZ-793A (Ki=8.29 μM). Analog 11f also showed similar potency of inhibition of [(3)H]-DA uptake into vesicles (Ki=45 nM) compared to that for GZ-793A (Ki=29 nM). Thus, 11f represents a new water-soluble inhibitor of VMAT function.

Exploring the Effect of N-Substitution In Nor-Lobelane On The Interaction With VMAT2: Discovery Of A Potential Clinical Candidate For Treatment Of Methamphetamine Abuse. Zheng G, Horton DB, Penthala NR, Nickell JR, Culver JP, Deaciuc AG, Dwoskin LP, Crooks PA. Medchemcomm. 2013 Mar; 4(3): 564-568.
A series of N-substituted lobelane analogues was synthesized and evaluated for their [3H]dihydrotetrabenazine binding affinity at the vesicular monoamine transporter and for their inhibition of vesicular [3H]dopamine uptake. Compound 19a, which contains an N-1,2(R)-dihydroxypropyl group, had been identified as a potential clinical candidate for the treatment of methamphetamine abuse.

Efficacy of Extended-Release Tramadol for Treatment of Prescription Opioid Withdrawal: A Two-Phase Randomized Controlled Trial. Lofwall MR, Babalonis S, Nuzzo PA, Siegel A, Campbell C, Walsh SL. Drug Alcohol Depend 2013 Jun, [Epub ahead of print].
Tramadol is an atypical analgesic with monoamine and modest mu opioid agonist activity. The purpose of this study was to evaluate: (1) the efficacy of extended-release (ER) tramadol in

treating prescription opioid withdrawal and (2) whether cessation of ER tramadol produces opioid withdrawal. Prescription opioid users with current opioid dependence and observed withdrawal participated in this inpatient two-phase double blind randomized placebo-controlled trial. In Phase 1 (days 1-7) participants were randomly assigned to matched oral placebo or ER tramadol (200 or 600mg daily). In Phase 2 (days 8-13) all participants underwent double blind crossover to placebo. Breakthrough withdrawal medications were available for all subjects. Enrollment continued until 12 completers/group was achieved. Use of breakthrough withdrawal medication differed significantly ($p<0.05$) among groups in both phases, the 200mg group received the least amount in Phase 1 and the 600mg group received the most in both phases. In Phase 1 tramadol 200mg produced significantly lower peak ratings than placebo on ratings of insomnia lacrimation muscular tension and sneezing. Only tramadol 600mg produced miosis in Phase 1. In Phase 2 tramadol 600mg produced higher peak ratings of rhinorrhea irritable depressed heavy/sluggish and hot/cold flashes than placebo. There were no serious adverse events and no signal of abuse liability for tramadol. The authors conclude that ER tramadol 200mg modestly attenuated opioid withdrawal. Mild opioid withdrawal occurred after cessation of treatment with 600mg tramadol. These data support the continued investigation of tramadol as a treatment for opioid withdrawal.

Determination of Oxycodone Noroxycodone and Oxymorphone By High-Performance Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry In Human Matrices: In Vivo and In Vitro Applications. Fang WB, Lofwall MR, Walsh SL, Moody DE. J Anal Toxicol 2013 Jun, [Epub ahead of print].
The opioid analgesic oxycodone is widely abused and increasingly associated with overdose deaths. A sensitive analytical method was developed for oxycodone and its metabolites noroxycodone and oxymorphone in human plasma urine (±enzymatic hydrolysis at 50°C for 16 h) and liver microsomes (HLMs). Liquid-liquid extraction was followed by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry. The calibration range was 0.2-250 ng/mL for plasma and HLM and 10-5000 ng/mL for urine. Intra- and interrun accuracies were within 13.3% of target, precisions were within 12.8% for all matrices. Recoveries from plasma were: oxycodone 75.6%, noroxycodone 37.4% and oxymorphone 18.2%. Analytes exhibited room temperature stability in plasma and urine up to 24 h and freeze-thaw stability in plasma up to three cycles. In 24-h hydrolyzed urine from subjects administered intranasal oxycodone (30 mg/70 kg n = 5) mean concentrations (ng/mL) and % daily doses excreted were: oxycodone 1150 6.53%, noroxycodone 1330 7.81% and oxymorphone 3000 17.1%. Oxycodone incubated with HLM produced more noroxycodone than oxymorphone with a panel of recombinant human cytochrome P450s (CYPs). CYP2C18 and CYP3A4 produced the most noroxycodone whereas CYP2D6 produced the most oxymorphone. These results demonstrate a new method suitable for both in vivo and in vitro metabolism and pharmacokinetic studies of oxycodone.

Effects of Prototypic Calcium Channel Blockers in Methadone-maintained Humans Responding Under a Naloxone Discrimination Procedure. Oliveto A, Mancino M, Sanders N, Cargile C, Benjamin Guise J, Bickel W, Brooks Gentry W. Eur J Pharmacol. 2013 Mar 21. pii: S0014-2999(13)00197-0. doi: 10.1016/j.ejphar.2013.03.007. [Epub ahead of print].
Accumulating evidence suggests that L-type calcium channel blockers (CCBs) attenuate the expression of opioid withdrawal and the dihydropyridine L-type CCB isradipine has been

shown to block the behavioral effects of naloxone in opioid-maintained humans. This study determined whether two prototypic L-type CCBs with differing chemical structures, the benzothiazepine diltiazem and the phenylalkamine verapamil, attenuate the behavioral effects of naloxone in methadone-maintained humans trained to distinguish between low-dose naloxone (0.15mg/70kg, i.m.) and placebo under an instructed novel-response drug discrimination procedure. Once discrimination was acquired, diltiazem (0, 30, 60, 120mg) and verapamil (0, 30, 60, 120mg), alone and combined with the training dose of naloxone, were tested. Diltiazem alone produced 33-50% naloxone- and novel-appropriate responding at 30 and 60mg and essentially placebo-appropriate responding at 120mg. Verapamil alone produced 20-40% naloxone- and 0% novel-appropriate responding. Diltiazem at 60mg decreased several ratings associated with positive mood and increased VAS ratings of "Bad Drug Effects" relative to placebo, whereas verapamil increased ratings associated with euphoria. When administered with naloxone, diltiazem produced 94-100% naloxone-appropriate-responding with 6% novel-appropriate responding at 60mg (n=3). When administered with naloxone, verapamil produced 60-80% naloxone- and 0% novel-appropriate responding (n=5). Diltiazem decreased diastolic blood pressure and heart rate whereas verapamil decreased ratings of arousal relative to placebo. These results suggest that CCBs with different chemical structures can be differentiated behaviorally, and that diltiazem and verapamil do not attenuate the discriminative stimulus effects of naloxone in humans at the doses tested.

Pilot Randomized Trial Of Bupropion For Adolescent Methamphetamine Abuse/Dependence. Heinzerling KG, Gadzhyan J, van Oudheusden H, Rodriguez F, McCracken J, Shoptaw S. J Adolesc Health. 2013 Apr; 52(4): 502-505. Epub 2013 Jan 17. The purpose of this study was to perform a pilot clinical trial of bupropion for methamphetamine abuse/dependence among adolescents. Nineteen adolescents with methamphetamine abuse (n = 2) or dependence (n = 17) were randomly assigned to bupropion SR 150 mg twice daily or placebo for 8 weeks with outpatient substance abuse counseling. Bupropion was well-tolerated except for one female in the bupropion group who was hospitalized for suicidal ideation during a methamphetamine relapse. Adolescents receiving bupropion and females provided significantly fewer methamphetamine-free urine tests compared to participants receiving placebo (p = .043) and males (p = .005) respectively. The authors conclude that their results do not support the feasibility of additional trials of bupropion for adolescent methamphetamine abuse/dependence. Future studies should investigate the influence of gender on adolescent methamphetamine abuse and treatment outcomes.

Effects of Acute Oral Naltrexone on the Subjective and Physiological Effects of Oral d-Amphetamine and Smoked Cocaine in Cocaine Abusers. Comer SD, Mogali S, Saccone PA, Askalsky P, Martinez D, Walker EA, Jones JD, Vosburg SK, Cooper ZD, Roux P, Sullivan MA, Manubay JM, Rubin E, Pines A, Berkower EL, Haney M, Foltin RW. Neuropsychopharmacology. 2013 Jun 5. doi: 10.1038/npp.2013.143. [Epub ahead of print]. Despite the prevalent worldwide abuse of stimulants, such as amphetamines and cocaine, no medications are currently approved for treating this serious public health problem. Both preclinical and clinical studies suggest that the opioid antagonist naltrexone (NTX) is effective in reducing the abuse liability of amphetamine, raising the question of whether similar positive

findings would be obtained for cocaine. The purpose of the present study was to evaluate the ability of oral NTX to alter the cardiovascular and subjective effects of d-amphetamine (AMPH) and cocaine (COC). Non-treatment-seeking COC users (N=12) completed this 3-week inpatient, randomized, crossover study. Participants received 0, 12.5, or 50 mg oral NTX 60 min prior to active or placebo stimulant administration during 10 separate laboratory sessions. Oral AMPH (0, 10, and 20 mg; or all placebo) was administered in ascending order within a laboratory session using a 60-min inter-dose interval. Smoked COC (0, 12.5, 25, and 50 mg; or all placebo) was administered in ascending order within a laboratory session using a 14-min inter-dose interval. Active COC and AMPH produced dose-related increases in cardiovascular function that were of comparable magnitude. In contrast, COC, but not AMPH, produced dose-related increases in several subjective measures of positive drug effect (e.g., high, liking, and willingness to pay for the drug). NTX did not alter the cardiovascular effects of AMPH or COC. NTX also did not alter positive subjective ratings after COC administration, but it did significantly reduce ratings of craving for cocaine and tobacco during COC sessions. These results demonstrate that (1) oral AMPH produces minimal abuse-related subjective responses in COC smokers, and (2) NTX reduces craving for COC and tobacco during COC sessions. Future studies should continue to evaluate NTX as a potential anti-craving medication for COC dependence.

Pharmacokinetic and Pharmacodynamic Profile of Supratherapeutic Oral Doses of Δ(9) -THC in Cannabis Users. Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR. J Clin Pharmacol 2013 Jul, (7): 680-690.

Oral Δ(9) -tetrahydrocannabinol (Δ(9) -THC) has been evaluated as a medication for cannabis dependence but repeated administration of acute oral doses up to 40 mg has not been effective at reducing drug-taking behavior. Larger doses might be necessary to affect cannabis use. The purpose of the present study was therefore to determine the physiological and behavioural effects of oral Δ(9) -THC at acute doses higher than those tested previously. The pharmacokinetic and pharmacodynamic profile of oral Δ(9) -THC administered in ascending order in 15 mg increments across separate sessions up to a maximum of 90 mg was determined in seven cannabis users. Five subjects received all doses and two experienced untoward side effects at lower doses. Δ(9) -THC produced a constellation of effects consistent with previous clinical studies. Low cannabinoid concentrations were associated with significant effects on drug-sensitive measures although progressively greater levels did not lead to proportionately larger drug effects. Considerable variability in Cmax and tmax was observed. Doses of oral Δ(9) -THC larger than those tested previously can be administered to individuals with a history of cannabis use although given the pharmacokinetic variability of oral Δ(9) -THC and individual differences in sensitivity individualized dose adjustment is needed to avoid side effects and maximize therapeutic response.

A Double-blind, Placebo-controlled Trial of Topiramate for the Treatment of Comorbid Cocaine and Alcohol Dependence. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. Drug Alcohol Depend. 2013 Jun 27. pii: S0376-8716(13)00201-9. doi: 10.1016/j.drugalcdep.2013.05.026. [Epub ahead of print].

Topiramate increases GABAergic activity and antagonizes the AMPA/kainate subtype of glutamate receptors. Through these mechanisms of action, topiramate may reduce alcohol and cocaine reward and may reduce alcohol and cocaine craving. Topiramate has been shown to

reduce drinking in persons with alcohol dependence, and reduce relapse in stimulant-dependent patients. The current trial was intended to test the ability of topiramate to promote cocaine and alcohol abstinence among patients addicted to both drugs. The study was a double-blind, placebo-controlled, 13-week trial involving 170 cocaine and alcohol dependent subjects. After achieving a period of cocaine and alcohol abstinence, subjects were randomized to topiramate, 300mg daily, or identical placebo capsules. In addition, subjects received weekly individual psychotherapy. Primary outcome measures included self-reported alcohol and cocaine use, and thrice weekly urine drug screens. Secondary outcome measures included cocaine and alcohol craving, Addiction Severity Index results, cocaine withdrawal symptoms, and clinical global improvement ratings. Results indicated that topiramate was not better than placebo in reducing cocaine use on the a priori primary outcome measure, or in reducing alcohol use. Topiramate was not better than placebo in reducing cocaine craving. Topiramate-treated subjects, compared to placebo-treated subjects, were more likely to be retained in treatment and more likely to be abstinent from cocaine during the last three weeks of the trial. Subjects who entered treatment with more severe cocaine withdrawal symptoms responded better to topiramate. The authors conclude that topiramate plus cognitive behavioral therapy may reduce cocaine use for some patients with comorbid cocaine and alcohol dependence.

Effects of Escitalopram on Attentional Bias to Cocaine-related Stimuli and Inhibitory Control in Cocaine-dependent Subjects. Liu S, Lane SD, Schmitz JM, Cunningham KA, John VP, Moeller FG. J Psychopharmacol. 2013 Jun 12. [Epub ahead of print].
Key characteristics of cocaine dependence include attentional bias to cocaine cues and impaired inhibitory control. Studies suggest that serotonin modulates both cocaine cue reactivity and inhibitory control. The authors investigated effects of the selective serotonin reuptake inhibitor escitalopram on cocaine cue reactivity and inhibitory processes in cocaine-dependent subjects. In a double-blind placebo-controlled design, cocaine-dependent subjects received placebo (n=12) or escitalopram (n=11; 10 mg on days 1-3, 20 mg on days 4-24 and 10 mg on days 25-28) orally, once daily for 4 weeks. The cocaine Stroop and immediate memory task (IMT) were administered at baseline, days 1, 4, 11, 18 and 25 after placebo or escitalopram initiation. There were no significant between-group differences in baseline performance on the cocaine Stroop task or the IMT. On day 1 (acute phase), escitalopram produced a significantly greater decrease from baseline than placebo in attentional bias measured by cocaine Stroop task 5 hours post-dose. No significant changes from baseline in attentional bias were observed on subsequent test days (chronic phase). Inhibitory control as measured by IMT commission error rate was not significantly different between two groups in either the acute or chronic phase. Consistent with preclinical data, serotonin-modulating drugs like escitalopram may have acute effects on cocaine cue reactivity in human cocaine users.

Cognitive Behavioral Therapy and the Nicotine Transdermal Patch for Dual Nicotine and Cannabis Dependence: a Pilot Study. Hill KP, Toto LH, Lukas SE, Weiss RD, Trksak GH, Rodolico JM, Greenfield SF. Am J Addict. 2013 May-Jun;22(3):233-8. doi: 10.1111/j.1521-0391.2012.12007.x. The authors assessed the feasibility of a new cognitive behavioral therapy (CBT) manual, plus transdermal patch nicotine replacement therapy (NRT), to treat co-occurring nicotine and cannabis dependence. Seven of 12 (58.3%) adults with DSM-IV diagnoses of both nicotine and cannabis dependence completed 10 weeks of individual CBT and NRT. Participants smoked 12.6 ± 4.9 tobacco cigarettes per day at

baseline, which was reduced to 2.1 ± 4.2 at the end of treatment ($F[5] = 23.5$, $p < .0001$). The reduction in cannabis use from 10.0 ± 5.3 inhalations per day at baseline to 8.0 ± 5.3 inhalations per day at 10 weeks was not significant ($F[5] = 1.12$, $p = .37$). There was a significant decrease from the mean baseline Fagerstrom Test for Nicotine Dependence scores at weeks 4, 6, 8, and 10 of treatment ($F[4] = 19.8$, $p < .001$) and mean Client Satisfaction Questionnaire scores were uniformly high (30.6 ± 1.9). The authors concluded that a CBT plus NRT treatment program significantly reduced tobacco smoking but did not significantly reduce cannabis use in individuals with co-occurring nicotine and cannabis dependence. There was no compensatory increase in cannabis use following the reduction in tobacco smoking, suggesting that clinicians can safely pursue simultaneous treatment of co-occurring nicotine and cannabis dependence. The intervention was well-liked by the 7 of the 12 enrollees who completed the study.

A Double-blind, Placebo-controlled Study of the Effects of Post-retrieval Propranolol on Reconsolidation of Memory for Craving and Cue Reactivity in Cocaine Dependent Humans. Saladin ME, Gray KM, McRae-Clark AL, Larowe SD, Yeatts SD, Baker NL, Hartwell KJ, Brady KT. Psychopharmacology (Berl). 2013 Apr;226(4):721-37. doi: 10.1007/s00213-013-3039-3. Epub 2013 Mar 5.

This study examined the effects of propranolol vs. placebo, administered immediately after a "retrieval" session of cocaine cue exposure (CCE), on craving and physiological responses occurring 24 h later during a subsequent "test" session of CCE. It was hypothesized that compared to placebo-treated cocaine-dependent (CD) individuals, propranolol-treated CD individuals would evidence attenuated craving and physiological reactivity during the test session. Secondarily, it was expected that group differences identified in the test session would be evident at a 1-week follow-up CCE session. Exploratory analyses of treatment effects on cocaine use were also performed at follow-up. CD participants received either 40 mg propranolol or placebo immediately following a "retrieval" CCE session. The next day, participants received a "test" session of CCE that was identical to the "retrieval" session except no medication was administered. Participants underwent a "follow-up" CCE session 1 week later. Craving and other reactivity measures were obtained at multiple time points during the CCE sessions. Propranolol- vs. placebo-treated participants evidenced significantly greater attenuation of craving and cardiovascular reactivity during the test session. Analysis of the follow-up CCE session data did not reveal any group differences. Although there was no evidence of treatment effects on cocaine use during follow-up, this study was insufficiently powered to rigorously evaluate differential cocaine use. This double-blind, placebo-controlled laboratory study provides the first evidence that propranolol administration following CCE may modulate memories for learning processes that subserve cocaine craving/cue reactivity in CD humans. Alternative interpretations of the findings were considered, and implications of the results for treatment were noted.

Association Of Abstinence-Induced Alterations In Working Memory Function and COMT Genotype In Smokers. Ashare RL, Valdez JN, Ruparel K, Albelda B, Hopson RD, Keefe JR, Loughead J. Lerman, C. Psychopharmacology (Berl) 2013 Jul; [Epub ahead of print].

The common methionine (met) for valine (val) at codon 158 (val(158)met) polymorphism in the catechol-O-methyltransferase (COMT) gene has been associated with nicotine dependence,

alterations in executive cognitive function, and abstinence-induced working memory deficits in smokers. The authors sought to replicate the association of the COMT val allele with abstinence-induced alterations in working memory-related activity in task-positive (executive control) and task-negative (default mode network) regions. Forty smokers (20 val/val and 20 met/met) performed an N-back task while undergoing blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) on two separate occasions: following 72 h of confirmed abstinence and during smoking as usual. An independent sample of 48 smokers who completed the identical N-back task during fMRI in smoking vs. abstinence for another study was used as a validation sample. Contrary to expectations, genotype by session interactions on BOLD signal in executive control regions (dorsolateral prefrontal cortex and dorsal cingulate/medial prefrontal cortex) revealed significant abstinence-induced reductions in the met/met group, but not the val/val group. Results also revealed that val/val smokers may exhibit less suppression of activation in task-negative regions such as the posterior cingulate cortex during abstinence (vs. smoking). These patterns were confirmed in the validation sample and in the whole-brain analysis, though the regions differed from the a priori regions of interest (ROIs) (e.g., precuneus, insula).The COMT val(158)met polymorphism was associated with abstinence-related working memory deficits in two independent samples of smokers. However, inconsistencies compared to prior findings and across methods (ROI vs. whole-brain analysis) highlight the challenges inherent in reproducing results of imaging genetic studies in addiction.

Gradual and Immediate Nicotine Reduction Result In Similar Low-Dose Nicotine Self-Administration. Smith TT, Levin ME, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Nicotine Tob Res 2013 Jul; [Epub ahead of print].

Food and Drug Administration-mandated product standards that drastically reduce nicotine content in cigarettes aim to result in decreased smoking and thus improved health outcomes for millions of U.S. smokers. Researchers have suggested that nicotine reduction should be implemented gradually, but a gradual nicotine reduction may shift the minimum level of nicotine required to reinforce behavior or may result in different levels of compensatory smoking behavior. Rats were given the opportunity to acquire nicotine self-administration at 60 µg/kg/infusion nicotine with a cocktail of other tobacco constituents included as the vehicle. Rats were subsequently assigned to one of six immediate dose reductions (30, 15, 7.5, 3.75, 1.875, or 0.0 µg/kg/infusion) for 10 sessions (n = 9-15). Rats in the 30 µg/kg/infusion reduction group continued to have their nicotine dose reduced by half after at least 10 sessions at each dose until reaching 1.875 µg/kg/infusion (i.e., gradual reduction). For both methods of reduction, reduction to 3.75 µg/kg/infusion resulted in significant decreases in behavior. Reduction to doses above 3.75 µg/kg/infusion resulted in only limited compensation. The largest compensation was temporary. There was no compensation following reduction to 3.75 µg/kg/infusion or below. This present study suggests that reduction to the same nicotine dose will result in similar reductions in behavior for both gradual and immediate reductions, and both methods result in similar compensation. Future studies using humans should investigate differences in other outcomes such as withdrawal and craving.

Sensitivity and Specificity Of A Procedure For Early Human Screening Of Novel Smoking Cessation Medications. Perkins KA, Lerman C, Karelitz JL, Jao NC, Chengappa KN, Sparks GM. Addiction 2013 Jun; [Epub ahead of print].
It is important to find economical methods in early Phase 2 studies to screen drugs potentially useful to aid smoking cessation. A method has been developed that detects efficacy of varenicline and nicotine patch. This study aimed to evaluate whether the method would detect efficacy of bupropion and correctly identify lack of efficacy of modafinil. Using a within-subject double crossover design, smokers attempted to quit during each treatment, with bupropion (150 mg b.i.d.), modafinil (100 mg b.i.d.), or placebo (double-blind, counter-balanced order). In each of three medication periods, all smoked with no drug on week 1 (baseline or washout), began dose run-up on week 2, and tried to quit every day during week 3. The study setting was a university research center in the United States. Participants were 45 adult smokers high in quit interest. Abstinence was verified daily each quit week by self-report of no smoking over the prior 24 hr and CO<5 ppm. Compared with placebo, bupropion did ($F(1,44)=6.98$, $p=.01$), but modafinil did not ($F(1,44)=.29$, $p=.60$), increase the number of abstinent days. Also, bupropion (versus placebo) significantly increased the number of those able to maintain continuous abstinence on all 5 days throughout the quit week (11 vs 4), $Z= 2.11$, $p <.05$, while modafinil did not (6). The authors conclude that assessing days abstinent during 1 week of use of medication versus placebo in a cross-over design could be a useful early Phase 2 study design for discriminating between medications useful vs not useful in aiding smoking cessation.

Effects Of Bupropion On Cognitive Performance During Initial Tobacco Abstinence. Perkins KA, Karelitz JL, Jao NC, Gur RC, Lerman, C. Drug Alcohol Depend 2013 May; [Epub ahead of print].
Bupropion may aid tobacco abstinence by quickly relieving symptoms of nicotine withdrawal, perhaps including impaired cognitive performance. The authors examined whether bupropion would attenuate abstinence-induced cognitive deficits on the first day of a brief quit attempt, when smokers are most likely to relapse. Smokers (N=24) with high quit interest were recruited for within-subjects cross-over test of bupropion vs placebo on ability to abstain during separate short-term practice quit smoking attempts. After introduction to working memory (N-back) and sustained attention (continuous performance task; CPT) tasks during the pre-quit smoking baseline, performance on these tasks was assessed after abstaining overnight (CO<10ppm) on the first day of each quit attempt, while on bupropion and on placebo. Compared to placebo, bupropion after abstinence improved correct response times for working memory ($p=.01$ for medication by memory load interaction) and for one measure of sustained attention (numbers, but not letters; $p<.05$). The authors conclude that bupropion may attenuate some features of impaired cognitive performance due to withdrawal on the first day of a quit attempt. Future studies could examine whether this effect of bupropion contributes to its efficacy for longer-term smoking cessation.

Naltrexone With Or Without Guanfacine For Preventing Relapse To Opiate Addiction In St. Petersburg, Russia. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Tsoy M, Wahlgren V, Burakov A, Masalov D, Romanova TN, Palatkin V, Tyurina A, Yaroslavtseva T, Sinha R, Kosten TR. Drug Alcohol Depend 2013 May; [Epub ahead of print].

Stress is a key precipitant to discontinuing naltrexone and relapsing to opiate abuse. Alpha-2 adrenergic agonists like guanfacine may reduce stress induced craving and have reduced opiate relapse in small clinical trials. This randomized, double blind double dummy placebo-controlled 6-month trial tested oral naltrexone with or without guanfacine for reducing stress and preventing opiate relapse. The authors randomized 301 patients to: naltrexone 50mg/day+guanfacine 1mg/day (n=75) (N/G), naltrexone+guanfacine placebo (N/P) (n=76), naltrexone placebo+guanfacine (n=75) (P/G), and double placebo (n=75) (P/P). Among the 75 patients in each group the percentage still retained on naltrexone treatment at six months was: N/G 26.7%, N/P 19.7% (p=0.258 to N/G), P/G 6.7% (p<0.05 to both N groups), and P/P 10.7% (p=0.013 to N+G). Guanfacine reduced the severity of stress particularly at weeks 10 and 18. Adverse events (AE) were infrequent (4.7%) without group differences, with most common AEs: headache, poor appetite, insomnia, and dizziness. The authors conclude that adding guanfacine to naltrexone did not improve treatment retention or opiate free urines, but it reduced both stress and craving at later time points in treatment, which may be related to stress-induced craving and the animal model of incubation of reinstatement. During treatment, HIV risk, anxiety, and depression reduced among all patients in treatment, regardless of group.

The First 7 Days Of A Quit Attempt Predicts Relapse: Validation Of A Measure For Screening Medications For Nicotine Dependence. Ashare RL, Wileyto EP, Perkins KA, Schnoll RA. J Addict Med 2013 May; [Epub ahead of print].
There is a critical need for the development of novel treatments for nicotine dependence. Because the majority of smokers who make a quit attempt fail within 7 days, medication screening procedures that focus on this early cessation period may provide an indicator of treatment efficacy. To establish the clinical validity of this paradigm, it is critical to demonstrate the association of early abstinence with longer-term abstinence. The authors tested the number of days of abstinence during the first week after the target quit date (TQD) as a predictor of point prevalence abstinence in 3 independent pharmacotherapy trials for nicotine dependence. This was a secondary data analysis of 3 randomized clinical trials: a placebo-controlled trial of transdermal nicotine (N = 545); an open-label nicotine replacement therapy (patch vs spray) trial (N = 566); and a bupropion placebo-controlled trial (N = 538). In separate logistic regression models, the maximum number of consecutive days of abstinence during the first week after the TQD was used to predict biochemically verified 7-day point prevalence abstinence at the end of treatment (EOT) and 6 months post-TQD. Across the 3 trials, the number of days of abstinence significantly predicted abstinence at EOT and 6 months (odds ratios > 1.4; Ps < 0.0001). Likewise, not having any lapse during the first week predicted abstinence at EOT and 6 months (odds ratios > 4.7; Ps < 0.0001). The authors conclude that the first week of abstinence was highly predictive of EOT and long-term abstinence. Medication screening procedures that focus on this early abstinence period (i.e., 6 or 7 days of consecutive abstinence) represent a valid tool for assessing the presence of a signal for medication efficacy.

The Ability Of Plasma Cotinine To Predict Nicotine and Carcinogen Exposure Is Altered By Differences In Cyp2A6: The Influence Of Genetics, Race, and Sex. Zhu AZ, Renner CC, Hatsukami DK, Swan GE, Lerman C, Benowitz NL, Tyndale RF. Cancer Epidemiol Biomarkers Prev 2013 Apr; (4): 708-718.
Cotinine, a nicotine metabolite, is a biomarker of tobacco, nicotine, and carcinogen exposure. However, a given cotinine level may not represent the same tobacco exposure; for example, African-Americans have higher cotinine levels than Caucasians after controlling for exposure. Cotinine levels are determined by the amount of cotinine formation and the rate of cotinine removal, which are both mediated by the enzyme CYP2A6. Because CYP2A6 activity differs by sex (estrogen induces CYP2A6) and genotype, their effect on cotinine formation and removal was measured in nonsmoking Caucasians (Study 1, n = 181) infused with labeled nicotine and cotinine. The findings were then extended to ad libitum smokers (Study 2, n = 163). Study 1: Reduced CYP2A6 activity altered cotinine formation less than cotinine removal resulting in ratios of formation to removal of 1.31 and 1.12 in CYP2A6 reduced and normal metabolizers (P = 0.01), or 1.39 and 1.12 in males and females (P = 0.001), suggesting an overestimation of tobacco exposure in slower metabolizers. Study 2: Cotinine again overestimated tobacco and carcinogen exposure by 25% or more in CYP2A6 reduced metabolizers (≈2-fold between some genotypes) and in males. In people with slower relative to faster CYP2A6 activity, cotinine accumulates resulting in substantial differences in cotinine levels for a given tobacco exposure. Cotinine levels may be misleading when comparing those with differing CYP2A6 genotypes within a race, between races with differing frequencies of CYP2A6 gene variants (i.e., African-Americans have higher frequencies of reduced function variants contributing to their higher cotinine levels), or between the sexes.

The DRD4 Exon III VNTR, Bupropion, and Associations With Prospective Abstinence. Bergen AW, Javitz HS, Su L, He Y, Conti DV, Benowitz NL, Tyndale RF, Lerman C, Swan GE. Nicotine Tob Res 2013 Jul; (7): 1190-1200.
DRD4 Exon III Variable Number of Tandem Repeat (VNTR) variation was found to interact with bupropion to influence prospective smoking abstinence, in a recently published longitudinal analyses of N = 331 individuals from a randomized double-blind placebo-controlled trial of bupropion and intensive cognitive-behavioral mood management therapy. The authors used univariate, multivariate, and longitudinal logistic regression to evaluate gene, treatment, time, and interaction effects on point prevalence and continuous abstinence at end of treatment, 6 months, and 12 months, respectively, in N = 416 European ancestry participants in a double-blind pharmacogenetic efficacy trial randomizing participants to active or placebo bupropion. Participants received 10 weeks of pharmacotherapy and 7 sessions of behavioral therapy, with a target quit date 2 weeks after initiating both therapies. VNTR genotypes were coded with the long allele dominant resulting in 4 analysis categories. Covariates included demographics, dependence measures, depressive symptoms, and genetic ancestry. The authors also performed genotype-stratified secondary analyses. They observed significant effects of time in longitudinal analyses of both abstinence outcomes, of treatment in individuals with VNTR long allele genotypes for both abstinence outcomes, and of covariates in some analyses. They observed non-significantly larger differences in active versus placebo effect sizes in individuals with VNTR long allele genotypes than in individuals without the VNTR long allele, in the directions previously reported. VNTR by treatment interaction differences between these and previous analyses may be attributable to insufficient size of the

replication sample. Analyses of multiple randomized clinical trials will enable identification and validation of factors mediating treatment response.

Two Decades Of Smoking Cessation Treatment Research On Smokers With Depression: 1990-2010. Weinberger AH, Mazure CM, Morlett A, McKee SA. Nicotine Tob Res 2013 Jun; (6): 1014-1031.

Adults with depression smoke at higher rates than other adults leaving a large segment of this population, who already incur increased health-related risks, vulnerable to the enormous harmful consequences of smoking. Yet, the impact that depression has on smoking cessation is not clear due to the mixed results of past research. The primary aims of this review were to synthesize the research examining the relationship of depression to smoking cessation outcomes over a 20-year period, to examine the gender and racial composition of these studies, and to identify directions for future research. Potential articles published between January 1, 1990 and December 31, 2010 were identified through a MEDLINE search of the terms "clinical trial," "depression," and "smoking cessation." 68 studies used all three terms and met the inclusion criteria. The majority of studies examined either a past diagnosis of major depression or current depression symptoms. Within the few studies that examined the interaction of gender and depression on smoking cessation, depression had a greater impact on treatment outcomes for women than men. No study reported examining the interactive impact of race and depression on treatment outcomes. Although attention to the relationship of depression and smoking cessation outcomes has increased over the past 20 years, little information exists to inform a treatment approach for smokers with Current Major Depressive Disorder, Dysthymia, and Minor Depression and few studies report gender and racial differences in the relationship of depression and smoking cessation outcomes, thus suggesting major areas for targeted research.

Brain Activity and Emotional Processing In Smokers Treated With Varenicline. Loughead J, Ray R, Wileyto EP, Ruparel K, O'Donnell GP, Senecal N, Siegel S, Gur RC, Lerman C. Addict Biol 2013 Jul; (4): 732-738.

Prior evidence suggests that varenicline, an effective smoking cessation treatment, may relieve negative affective signs of nicotine withdrawal. The authors examined varenicline effects on emotional processing in 25 abstinent smokers after 13 days of varenicline and placebo using a within-subject cross-over design. Blood oxygen level dependent (BOLD) functional magnetic resonance imaging was acquired while subjects completed a face emotion identification task. Results showed a significant drug effect, characterized by decreased BOLD signal in dorsal anterior cingulate/medial frontal cortex, occipital cortex and thalamus. Increased BOLD signal was observed in the middle temporal gyrus. Varenicline improved correct response time; however, neither BOLD signal nor performance effects were moderated by emotion type. An exploratory region of interest analysis suggests that varenicline reduced amygdala activity independent of emotional valence. Taken together, these results suggest that observed drug effects on brain activity do not reflect affective changes but rather enhanced early processing of perceptual features of facial stimuli.

Adenovirus Capsid-Based Anti-Cocaine Vaccine Prevents Cocaine from Binding to the Nonhuman Primate CNS Dopamine Transporter. Maoz A, Hicks MJ, Vallabhjosula S, Synan M, Kothari PJ, Dyke JP, Ballon DJ, Kaminsky SM, De BP, Rosenberg JB, Martinez D, Koob GF, Janda KD, Crystal RG. Neuropsychopharmacology. 2013 May 10.
Cocaine addiction is a major problem for which there is no approved pharmacotherapy. The authors have developed a vaccine to cocaine (dAd5GNE), based on the cocaine analog GNE linked to the capsid proteins of a serotype 5 adenovirus, designed to evoke anti-cocaine antibodies that sequester cocaine in the blood, preventing access to the CNS. To assess the efficacy of dAd5GNE in a large animal model, positron emission tomography (PET) and the radiotracer [11C]PE2I were used to measure cocaine occupancy of the dopamine transporter (DAT) in nonhuman primates. Repeat administration of dAd5GNE induced high anti-cocaine titers. Before vaccination, cocaine displaced PE2I from DAT in the caudate and putamen, resulting in 62±4% cocaine occupancy. In contrast, dAd5GNE-vaccinated animals showed reduced cocaine occupancy such that when anti-cocaine titers were >4 × 105, the cocaine occupancy was reduced to levels of <20%, significantly below the 47% threshold required to evoke the subjective 'high' reported in humans.

Liposomes Containing Monophosphoryl Lipid A: A Potent Adjuvant System For Inducing Antibodies To Heroin Hapten Analogs. Matyas GR, Mayorov AV, Rice KC, Jacobson AE, Cheng K, Iyer MR, Li F, Beck Z, Janda KD, Alving CR. Vaccine. 2013 Jun 10; 31(26): 2804-2810. In order to create an effective immunization approach for a potential vaccine to heroin, liposomes containing monophosphoryl lipid A [L(MPLA)] were tested as an adjuvant system to induce antibodies to heroin hapten analogs. Four synthetic haptens and two immunization strategies were employed. In the first strategy, a hydrophobic 23 amino acid immunogenic peptide derived from the membrane proximal external region of gp41 from HIV-1 envelope protein was embedded as a carrier in the outer surface of L(MPLA), to which was conjugated a 15 amino acid universal T cell epitope and a terminal heroin hapten analog. In the second strategy, tetanus toxoid (TT) carrier protein was decorated with haptens by conjugation, and the hapten-conjugated protein was mixed with L(MPLA). After immunization of mice, each of the immunization strategies was effective for induction of IgG anti-hapten antibodies. The first immunization strategy induced a mean end-point IgG titer against one of two haptens tested of approximately 12,800; however, no detectable antibodies were induced against the liposome-associated HIV-1 carrier peptide. In the second immunization strategy, depending on the hapten used for decorating the TT, end-point IgG titers ranged from 100,000 to 6,500,000. In this strategy, in which hapten was conjugated to the TT, end-point IgG titers of 400,000 to the TT carrier were observed with each conjugate. However, upon mixing unconjugated TT with L(MPLA), anti-TT titers of 6,500,000 were observed. The authors conclude that L(MPLA) serves as a potent adjuvant for inducing antibodies to candidate heroin haptens. However, antibodies to the carrier peptide or protein were partly or completed inhibited by the presence of conjugated hapten.

Suppression Of Nicotine-Induced Pathophysiology By An Adenovirus Hexon-Based Antinicotine Vaccine. Rosenberg JB, De BP, Hicks MJ, Janda KD, Kaminsky SM, Worgall S, Crystal RG. Hum Gene Ther. 2013 Jun; 24(6): 595-603.
Despite antismoking campaigns, cigarette smoking remains a pervasive addiction with significant societal impact, accounting for one of every five deaths. Smoking cessation

therapies to help smokers quit are ineffective with a high recidivism rate. With the knowledge that nicotine is the principal addictive compound of cigarettes, the authors have developed an antismoking vaccine based on the highly immunogenic properties of the hexon protein purified from the serotype 5 adenovirus (Ad) capsid. They hypothesized that an effective antinicotine vaccine could be based on coupling the nicotine hapten AM1 to purified Ad hexon protein. To assess this, AM1 was conjugated to hexon purified from serotype 5 Ad to produce the HexonAM1 vaccine. C57Bl/6 mice were sensitized by 10 daily nicotine administrations (0.5 mg/kg, subcutaneous) to render the mice addicted to nicotine. Control groups were sensitized to phosphate-buffered saline (PBS). The mice were then immunized with HexonAM1 (4 μg, intramuscular) at 0, 3, and 6 weeks. By 6 weeks, the HexonAM1-vaccinated mice had serum antinicotine antibody titers of 1.1×10(6)±7.6×10(4). To demonstrate that these high antinicotine titers were sufficient to suppress the effects of nicotine, HexonAM1-vaccinated mice were evaluated for nicotine-induced hypoactive behavior with nicotine challenges (0.5 mg/kg wt) over 5 weeks. In all challenges, the HexonAM1-vaccinated mice behaved similar to PBS-challenged naive mice. These data demonstrate that a vaccine comprised of a nicotine analog coupled to Ad hexon can evoke a high level of antinicotine antibodies sufficient to inhibit nicotine-induced behavior. The HexonAM1 vaccine represents a platform paradigm for vaccines against small molecules.

Effects of 14-Day Treatment with the Schedule III Anorectic Phendimetrazine on Choice between Cocaine and Food in Rhesus Monkeys. Banks ML, Blough BE, Negus SS. Drug Alcohol Depend. 2013 May 30. pii: S0376-8716(13)00180-4.

The clinical utility of monoamine releasers such as phenmetrazine or d-amphetamine as candidate agonist medications for cocaine dependence is hindered by their high abuse liability. Phendimetrazine is a clinically available schedule III anorectic that functions as a prodrug for phenmetrazine and thus may have lower abuse liability. This study determined the effects of continuous 14-day treatment with phendimetrazine on cocaine vs. food choice in rhesus monkeys (N=4). Responding was maintained under a concurrent schedule of food delivery (1-g pellets, fixed-ratio 100 schedule) and cocaine injections (0-0.1mg/kg/injection, fixed-ratio 10 schedule). Cocaine choice dose-effect curves were determined daily before and during 14-day periods of continuous intravenous treatment with saline or (+)-phendimetrazine (0.32-1.0mg/kg/h). Effects of 14-day treatment with (+)-phenmetrazine (0.1-0.32mg/kg/h; N=5) and d-amphetamine (0.032-0.1mg/kg/h; N=6) were also examined for comparison. During saline treatment, food was primarily chosen during availability of low cocaine doses (0, 0.0032, and 0.01mg/kg/injection), and cocaine was primarily chosen during availability of higher cocaine doses (0.032 and 0.1mg/kg/injection). Phendimetrazine initially decreased overall responding without significantly altering cocaine choice. Over the course of 14 days, tolerance developed to rate decreasing effects, and phendimetrazine dose-dependently decreased cocaine choice (significant at 0.032mg/kg/injection cocaine). Phenmetrazine and d-amphetamine produced qualitatively similar effects. These results demonstrate that phendimetrazine can produce significant, though modest, reductions in cocaine choice in rhesus monkeys. Phendimetrazine may be especially suitable as a candidate medication for human studies because of its schedule III clinical availability.

Molecular and Behavioral Pharmacology of Two Novel Orally-Active 5HT2 Modulators: Potential Utility as Antipsychotic Medications. Morgan D, Kondabolu K, Kuipers A, Sakhuja R, Robertson KL, Rowland NE, Booth RG. Neuropharmacology. 2013 May 9; 72C: 274-281.

Desired serotonin 5HT2 receptor pharmacology for treatment of psychoses is 5HT2A antagonism and/or 5HT2C agonism. No selective 5HT2A antagonist has been approved for psychosis and the only approved 5HT2C agonist (for obesity) also activates 5HT2A and 5HT2B receptors, which can lead to clinical complications. Studies herein tested the hypothesis that a dual-function 5HT2A antagonist/ 5HT2C agonist that does not activate 5HT2B receptors would be suitable for development as an antipsychotic drug, without liability for weight gain. The novel compounds (+)- and (-)-trans-4-(4'-chlorophenyl)-N,N-dimethyl-2-aminotetralin (p-Cl-PAT) were synthesized, characterized in vitro for affinity and functional activity at human 5HT2 receptors, and administered by intraperitoneal (i.p.) and oral (gavage) routes to mice in behavioral paradigms that assessed antipsychotic efficacy and effects on feeding behavior. (+)- and (-)-p-Cl-PAT activated 5HT2C receptors, with (+)-p-Cl-PAT being 12-times more potent, consistent with its higher affinity across 5HT2 receptors. Neither p-Cl-PAT enantiomer activated 5HT2A or 5HT2B receptors at concentrations up to 300-times greater than their respective affinity (K_i), and (+)-p-Cl-PAT was shown to be a 5HT2A competitive antagonist. When administered i.p. or orally, (+)- and (-)-p-Cl-PAT attenuated the head-twitch response (HTR) in mice elicited by the 5HT2 agonist (-)-2,5-dimethoxy-4-iodoamphetamine (DOI) and reduced intake of a highly palatable food in non-food-deprived mice, with (+)-p-Cl-PAT being more potent across behavioral assays. The novel in vitro pharmacology of (+)-p-Cl-PAT (5HT2A antagonism/5HT2C agonism without activation of 5HT2B) translated in vivo to an orally-active drug candidate with preclinical efficacy to treat psychoses without liability for weight gain.

SN79, A Sigma Receptor Ligand, Blocks Methamphetamine-Induced Microglial Activation and Cytokine Upregulation. Robson MJ, Turner RC, Naser ZJ, McCurdy CR, Huber JD, Matsumoto RR. Exp Neurol. 2013 Apr 28; 247C: 134-142.

Methamphetamine (METH) abuse is associated with several negative side effects including neurotoxicity in specific brain regions such as the striatum. The precise molecular mechanisms by which METH usage results in neurotoxicity remain to be fully elucidated, with recent evidence implicating the importance of microglial activation and neuroinflammation in damaged brain regions. METH interacts with sigma receptors which are found in glial cells in addition to neurons. Moreover, sigma receptor antagonists have been shown to block METH-induced neurotoxicity in rodents although the cellular mechanisms underlying their neuroprotection remain unknown. The purpose of the current study was to determine if the prototypic sigma receptor antagonist, SN79, mitigates METH-induced microglial activation and associated increases in cytokine expression in a rodent model of METH-induced neurotoxicity. METH increased striatal mRNA and protein levels of cluster of differentiation 68 (CD68), indicative of microglial activation. METH also increased ionized calcium binding adapter molecule 1 (IBA-1) protein expression, further confirming the activation of microglia. Along with microglial activation, METH increased striatal mRNA expression levels of IL-6 family pro-inflammatory cytokines, leukemia inhibitory factor (lif), oncostatin m (osm), and interleukin-6 (il-6). Pretreatment with SN79 reduced METH-induced increases in CD68 and IBA-1 expression, demonstrating its ability to prevent microglial activation. SN79 also

attenuated METH-induced mRNA increases in IL-6 pro-inflammatory cytokine family members. The ability of a sigma receptor antagonist to block METH-induced microglial activation and cytokine production provides a novel mechanism through which the neurotoxic effects of METH may be mitigated.

Probing Active Cocaine Vaccination Performance Through Catalytic and Noncatalytic Hapten Design. Cai X, Whitfield T, Hixon MS, Grant Y, Koob GF, Janda KD. J Med Chem. 2013 May 9; 56(9): 3701-3709.
Presently, there are no FDA-approved medications to treat cocaine addiction. Active vaccination has emerged as one approach to intervene through the rapid sequestering of the circulating drug, thus terminating both psychoactive effects and drug toxicity. Herein, the authors report their efforts examining two complementary, but mechanistically distinct active vaccines, i.e., noncatalytic and catalytic, for cocaine treatment. A cocaine-like hapten GNE and a cocaine transition-state analogue GNT were used to generate the active vaccines, respectively. GNE-KLH (keyhole limpet hemocyannin) was found to elicit persistent high-titer, cocaine-specific antibodies and blunt cocaine-induced locomotor behaviors. Catalytic antibodies induced by GNT-KLH were also shown to produce potent titers and suppress locomotor response in mice; however, upon repeated cocaine challenges, the vaccine's protecting effects waned. In depth kinetic analysis suggested that loss of catalytic activity was due to antibody modification by cocaine. The work provides new insights for the development of active vaccines for the treatment of cocaine abuse.

Evaluation of N-Phenyl Homopiperazine Analogs as Potential Dopamine D3 Receptor Selective Ligands. Li A, Mishra Y, Malik M, Wang Q, Li S, Taylor M, Reichert DE, Luedtke RR, Mach RH. Bioorg Med Chem. 2013 Jun 1; 21(11): 2988-2998.
A series of N-(2-methoxyphenyl)homopiperazine analogs was prepared and their affinities for dopamine D2, D3, and D4 receptors were measured using competitive radioligand binding assays. Several ligands exhibited high binding affinity and selectivity for the D3 dopamine receptor compared to the D2 receptor subtype. Compounds 11a, 11b, 11c, 11f, 11j and 11k had K(i) values ranging from 0.7 to 3.9 nM for the D3 receptor with 30- to 170-fold selectivity for the D3 versus D2 receptor. Calculated logP values (logP=2.6-3.6) are within the desired range for passive transport across the blood-brain barrier. When the binding and the intrinsic efficacy of these phenylhomopiperazines were compared to those of previously published phenylpiperazine analogues, it was found that (a) affinity at D2 and D3 dopamine receptors generally decreased, (b) the D3 receptor binding selectivity (D2:D3 K(i) value ratio) decreased and, (c) the intrinsic efficacy, measured using a forskolin-dependent adenylyl cyclase inhibition assay, generally increased.

Acquisition of Responding with a Remifentanil-Associated Conditioned Reinforcer in the Rat. Bertz JW, Woods JH. Psychopharmacology (Berl). 2013 Apr 23.
Drug-associated environmental stimuli may serve as conditioned reinforcers to enhance drug self-administration behaviors in humans and laboratory animals. However, it can be difficult to distinguish experimentally the conditioned reinforcing effects of a stimulus from other behavioral processes that can change rates of responding. To characterize the conditioned reinforcing effects of a stimulus paired with the μ-opioid agonist, remifentanil, using a new-response acquisition procedure in the rat. First, in Pavlovian conditioning (PAV) sessions, rats

received response-independent IV injections of remifentanil and presentations of a light-noise compound stimulus. In paired PAV groups, injections and stimulus presentations always co-occurred. In random PAV control groups, injections and stimulus presentations occurred with no consistent relationship. Second, in instrumental acquisition (ACQ) sessions, all animals could respond in an active nose-poke that produced the stimulus alone or in an inactive nose-poke that had no scheduled consequences. During ACQ, rats made significantly more active nose-pokes than inactive nose-pokes after paired PAV, but not after random PAV. Between groups, rats also made more active nose-pokes after paired PAV than after random PAV. After paired PAV, increased active responding was obtained under different schedules of reinforcement, persisted across multiple ACQ sessions, and depended on the number of PAV sessions conducted. The remifentanil-paired stimulus served as a conditioned reinforcer for nose-poking: responding depended on both the contingency between the stimulus and remifentanil and the contingency between the nose-poke and the stimulus. Generally, new-response acquisition procedures may provide valid, flexible models for studying opioid-based conditioned reinforcement.

Probing the Metabotropic Glutamate Receptor 5 ($Mglu_5$) Positive Allosteric Modulator (PAM) Binding Pocket: Discovery of Point Mutations that Engender a "Molecular Switch" in PAM Pharmacology. Gregory KJ, Nguyen ED, Reiff SD, Squire EF, Stauffer SR, Lindsley CW, Meiler J, Conn PJ. Mol Pharmacol. 2013 May; 83(5): 991-1006. Positive allosteric modulation of metabotropic glutamate receptor subtype 5 ($mGlu_5$) is a promising novel approach for the treatment of schizophrenia and cognitive disorders. Allosteric binding sites are topographically distinct from the endogenous ligand (orthosteric) binding site, allowing for co-occupation of a single receptor with the endogenous ligand and an allosteric modulator. Negative allosteric modulators (NAMs) inhibit and positive allosteric modulators (PAMs) enhance the affinity and/or efficacy of the orthosteric agonist. The molecular determinants that govern $mGlu_5$ modulator affinity versus cooperativity are not well understood. Focusing on the modulators based on the acetylene scaffold, the authors sought to determine the molecular interactions that contribute to PAM versus NAM pharmacology. Generation of a comparative model of the transmembrane-spanning region of $mGlu_5$ served as a tool to predict and interpret the impact of mutations in this region. Application of an operational model of allosterism allowed for determination of PAM and NAM affinity estimates at receptor constructs that possessed no detectable radioligand binding as well as delineation of effects on affinity versus cooperativity. Novel mutations within the transmembrane domain (TM) regions were identified that had differential effects on acetylene PAMs versus 2-methyl-6-(phenylethynyl)-pyridine, a prototypical NAM. Three conserved amino acids (Y658, T780, and S808) and two nonconserved residues (P654 and A809) were identified as key determinants of PAM activity. Interestingly, the authors identified two point mutations in TMs 6 and 7 that, when mutated, engender a mode switch in the pharmacology of certain PAMs.

Redefining the Structure-Activity Relationships of 2,6-Methano-3-Benzazocines. Part 9: Synthesis, Characterization and Molecular Modeling of Pyridinyl Isosteres of N-BPE-8-CAC (1), a High Affinity Ligand for Opioid Receptors. VanAlstine MA, Wentland MP, Alvarez J, Cao Q, Cohen DJ, Knapp BI, Bidlack JM. Bioorg Med Chem Lett. 2013 Apr 1; 23(7): 2128-2133.

Derivatives of the lead compound N-BPE-8-CAC (1) where each CH of the biphenyl group was individually replaced by N were prepared in hopes of identifying high affinity ligands with improved aqueous solubility. Compared to 1, binding affinities of the five possible pyridinyl derivatives for the μ opioid receptor were between threefold lower to fivefold higher with the Ki of the most potent compound being 0.064 nM. Docking of 8-CAC (2) into the unliganded binding site of the mouse μ opioid receptor (pdb: 4DKL) revealed that 8-CAC and β-FNA (from 4DKL) make nearly identical interactions with the receptor. However, for 1 and the new pyridinyl derivatives 4-8, binding is not tolerated in the 8-CAC binding mode due to the steric constraints of the large N-substituents. Either an alternative binding mode or rearrangement of the protein to accommodate these modifications may account for their high binding affinity.

A Novel Metabotropic Glutamate Receptor 5 Positive Allosteric Modulator Acts at a Unique Site and Confers Stimulus Bias to mGlu5 Signaling. Noetzel MJ, Gregory KJ, Vinson PN, Manka JT, Stauffer SR, Lindsley CW, Niswender CM, Xiang Z, Conn PJ. Mol Pharmacol. 2013 Apr; 83(4): 835-847.

Metabotropic glutamate receptor 5 (mGlu5) is a target for the treatment of central nervous system (CNS) disorders, such as schizophrenia and Alzheimer's disease. Furthermore, mGlu5 has been shown to play an important role in hippocampal synaptic plasticity, specifically in long-term depression (LTD) and long-term potentiation (LTP), which is thought to be involved in cognition. Multiple mGlu5-positive allosteric modulators (PAMs) have been developed from a variety of different scaffolds. Previous work has extensively characterized a common allosteric site on mGlu5, termed the MPEP (2-Methyl-6-(phenylethynyl)pyridine) binding site. However, one mGlu5 PAM, CPPHA (N-(4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl)-2-hydroxybenzamide), interacts with a separate allosteric site on mGlu5. Using cell-based assays and brain slice preparations, the authors characterized the interaction of a potent and efficacious mGlu5 PAM from the CPPHA series termed NCFP (N-(4-chloro-2-((4-fluoro-1,3-dioxoisoindolin-2-yl)methyl)phenyl)picolinamide). NCFP binds to the CPPHA site on mGlu5 and potentiates mGlu5-mediated responses in both recombinant and native systems. However, NCFP provides greater mGlu5 subtype selectivity than does CPPHA, making it more suitable for studies of effects on mGlu5 in CNS preparations. Of interest, NCFP does not potentiate responses involved in hippocampal synaptic plasticity (LTD/LTP), setting it apart from other previously characterized MPEP site PAMs. This suggests that although mGlu5 PAMs may have similar responses in some systems, they can induce differential effects on mGlu5-mediated physiologic responses in the CNS. Such stimulus bias by mGlu5 PAMs may complicate drug discovery efforts but would also allow for specifically tailored therapies, if pharmacological biases can be attributed to different therapeutic outcomes.

Positron Emission Tomography Imaging of Dopamine D2 Receptors Using a Highly Selective Radiolabeled D2 Receptor Partial Agonist. Xu J, Vangveravong S, Li S, Fan J, Jones LA, Cui J, Wang R, Tu Z, Chu W, Perlmutter JS, Mach RH. Neuroimage. 2013 May 1; 71: 168-174.

A series of microPET imaging studies were conducted in anesthetized rhesus monkeys using the dopamine D2-selective partial agonist, [(11)C]SV-III-130. There was a high uptake in regions of brain known to express a high density of D2 receptors under baseline conditions.

Rapid displacement in the caudate and putamen, but not in the cerebellum, was observed after injection of the dopamine D2/3 receptor nonselective ligand S(-)-eticlopride at a low dosage (0.025mg/kg/i.v.); no obvious displacement in the caudate, putamen and cerebellum was observed after the treatment with a dopamine D3 receptor selective ligand WC-34 (0.1mg/kg/i.v.). Pretreatment with lorazepam (1mg/kg, i.v. 30min) to reduce endogenous dopamine prior to tracer injection resulted in unchanged binding potential (BP) values, a measure of D2 receptor binding in vivo, in the caudate and putamen. d-Amphetamine challenge studies indicate that there is a significant displacement of [(11)C]SV-III-130 by d-Amphetamine-induced increases in synaptic dopamine levels.

Catalytic Mechanism of Cytochrome P450 for N-Methylhydroxylation of Nicotine: Reaction Pathways and Regioselectivity of the Enzymatic Nicotine Oxidation. Li D, Huang X, Lin J, Zhan CG. Dalton Trans. 2013 Mar 21; 42(11): 3812-3820.
The fundamental reaction mechanism of cytochrome P450 2A6 (CYP2A6)-catalyzed N-methylhydroxylation of (S)-(-)-nicotine and the free energy profile have been studied by performing pseudobond first-principles quantum mechanical/molecular mechanical (QM/MM) reaction-coordinate calculations. In the CYP2A6-(S)-(-)-nicotine binding structures that allow for 5'-hydroxylation, the N-methyl group is also sufficiently close to the oxygen of Cpd I for the N-methylhydroxylation reaction to occur. It has been demonstrated that the CYP2A6-catalyzed N-methylhydroxylation reaction is a concerted process involving a hydrogen-transfer transition state on both the quartet and the doublet states. The N-methylhydroxylation reaction proceeds mainly in the doublet state, since the free energy barriers on the doublet state are lower than the corresponding ones on the quartet state. The calculated free energy barriers indicate that (S)-(-)-nicotine oxidation catalyzed by CYP2A6 proceeds with a high regioselective abstraction of the hydrogen at the 5'-position, rather than the hydrogen at the N-methyl group. The predicted regioselectivity of 93% is in agreement with the most recent experimentally reported regioselectivity of 95%. The binding mode of (S)-(-)-nicotine in the active site of CYP2A6 is an important determinant for the stereoselectivity of nicotine (S)-(-)-oxidation, whereas the regioselectivity of (S)-(-)-nicotine oxidation is determined mainly by the free energy barrier difference between the 5'-hydroxylation and N-methylhydroxylation reactions.

Role of Phenmetrazine as an Active Metabolite of Phendimetrazine: Evidence from Studies of Drug Discrimination and Pharmacokinetics In Rhesus Monkeys. Banks ML, Blough BE, Fennell TR, Snyder RW, Negus SS. Drug Alcohol Depend. 2013 Jun 1; 130(1-3): 158-166. Monoamine releasers such as d-amphetamine that selectively promote release of dopamine/norepinephrine versus serotonin are one class of candidate medications for treating cocaine dependence; however, their clinical utility is limited by undesirable effects such as abuse liability. Clinical utility of these compounds may be increased by development of prodrugs to reduce abuse potential by slowing onset of drug effects. This study examined the behavioral and pharmacokinetic profile of the Schedule III compound phendimetrazine, which may serve as a prodrug for the N-demethylated metabolite and potent dopamine/norepinephrine releaser phenmetrazine. Monkeys (n = 5) were trained in a two-key food-reinforced discrimination procedure to discriminate cocaine (0.32 mg/kg, IM) from saline, and the potency and time course of cocaine-like discriminative stimulus effects were determined for (+)-phenmetrazine, (-)-phenmetrazine, (+)-phendimetrazine, (-)-

phendimetrazine, and (±)-phendimetrazine. Parallel pharmacokinetic studies in the same monkeys examined plasma phenmetrazine and phendimetrazine levels for correlation with cocaine-like discriminative stimulus effects. Both isomers of phenmetrazine, and the racemate and both isomers of phendimetrazine, produced dose- and time-dependent substitution for the discriminative stimulus effects of cocaine, with greater potency residing in the (+) isomers. In general, plasma phenmetrazine levels increased to similar levels after administration of behaviorally active doses of either phenmetrazine or phendimetrazine. These results support the hypothesis that phenmetrazine is an active metabolite that contributes to the effects of phendimetrazine. However, behavioral effects of phendimetrazine had a more rapid onset than would have been predicted by phenmetrazine levels alone, suggesting that other mechanisms may also contribute.

Reduction in Phencyclidine Induced Sensorimotor Gating Deficits in the Rat Following Increased System Xc(-) Activity in the Medial Prefrontal Cortex. Lutgen V, Qualmann K, Resch J, Kong L, Choi S, Baker DA. Psychopharmacology (Berl). 2013 Apr; 226(3): 531-540. Aspects of schizophrenia, including deficits in sensorimotor gating, have been linked to glutamate dysfunction and/or oxidative stress in the prefrontal cortex. System xc(-), a cystine-glutamate antiporter, is a poorly understood mechanism that contributes to both cellular antioxidant capacity and glutamate homeostasis. The authors' goal was to determine whether increased system xc(-) activity within the prefrontal cortex would normalize a rodent measure of sensorimotor gating. In situ hybridization was used to map messenger RNA (mRNA) expression of xCT, the active subunit of system xc(-), in the prefrontal cortex. Prepulse inhibition was used to measure sensorimotor gating; deficits in prepulse inhibition were produced using phencyclidine (0.3-3 mg/kg, sc). N-Acetylcysteine (10-100 μM) and the system xc(-) inhibitor (S)-4-carboxyphenylglycine (CPG, 0.5 μM) were used to increase and decrease system xc(-) activity, respectively. The uptake of (14)C-cystine into tissue punches obtained from the prefrontal cortex was used to assay system xc(-) activity. The expression of xCT mRNA in the prefrontal cortex was most prominent in a lateral band spanning primarily the prelimbic cortex. Although phencyclidine did not alter the uptake of (14)C-cystine in prefrontal cortical tissue punches, intraprefrontal cortical infusion of N-acetylcysteine (10-100 μM) significantly reduced phencyclidine- (1.5 mg/kg, sc) induced deficits in prepulse inhibition. N-Acetylcysteine was without effect when coinfused with CPG (0.5 μM), indicating an involvement of system xc(-). These results indicate that phencyclidine disrupts sensorimotor gating through system xc(-) independent mechanisms, but that increasing cystine-glutamate exchange in the prefrontal cortex is sufficient to reduce behavioral deficits produced by phencyclidine.

Catalytic Activities of a Cocaine Hydrolase Engineered from Human Butyrylcholin-esterase Against (+)- and (-)-Cocaine. Xue L, Hou S, Yang W, Fang L, Zheng F, Zhan CG. Chem Biol Interact. 2013 Mar 25; 203(1): 57-62.
It can be argued that an ideal anti-cocaine medication would be one that accelerates cocaine metabolism producing biologically inactive metabolites via a route similar to the primary cocaine-metabolizing pathway, i.e., hydrolysis catalyzed by butyrylcholinesterase (BChE) in plasma. However, wild-type BChE has a low catalytic efficiency against naturally occurring (-)-cocaine. Interestingly, wild-type BChE has a much higher catalytic activity against unnatural (+)-cocaine. According to available positron emission tomography (PET) imaging analysis

using [(11)C](-)-cocaine and [(11)C](+)-cocaine tracers in human subjects, only [(11)C](-)-cocaine was observed in the brain, whereas no significant [(11)C](+)-cocaine signal was observed in the brain. The available PET data imply that an effective therapeutic enzyme for treatment of cocaine abuse could be an exogenous cocaine-metabolizing enzyme with a catalytic activity against (-)-cocaine comparable to that of wild-type BChE against (+)-cocaine. The authors' recently designed A199S/F227A/S287G/ A328 W/Y332G mutant of human BChE has a considerably improved catalytic efficiency against (-)-cocaine and has been proven active in vivo. In the present study, the authors have characterized the catalytic activities of wild-type BChE and the A199S/F227A/S287G/A328 W/Y332G mutant against both (+)- and (-)-cocaine at the same time under the same experimental conditions. Based on the obtained kinetic data, the A199S/F227A/S287G/A328 W/Y332G mutant has a similarly high catalytic efficiency (kcat/KM) against (+)- and (-)-cocaine, and indeed has a catalytic efficiency (k(cat/)K(M) = 1.84 × 10(9) M(-1) min(-1)) against (-)-cocaine comparable to that (k(cat)/K(M) = 1.37 × 10(9) M(-1) min(-1)) of wild-type BChE against (+)-cocaine. Thus, the mutant may be used to effectively prevent (-)-cocaine from entering brain and producing physiological effects in the enzyme-based treatment of cocaine abuse.

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Human Synaptic Plasticity Gene Expression Profile and Dendritic Spine Density Changes In HIV-Infected Human CNS Cells: Role In HIV-Associated Neurocognitive Disorders (HAND). Atluri VS, Kanthikeel SP, Reddy PV, Yndart A, Nair MP. PLoS One. 2013 Apr 19; 8(4): e61399. doi: 10.1371/journal.pone.0061399.

HIV-associated neurocognitive disorders (HAND) is characterized by development of cognitive, behavioral and motor abnormalities, and occur in approximately 50% of HIV infected individuals. Current understanding of HAND emanates mainly from HIV-1 subtype B (clade B), which is prevalent in USA and Western countries. However very little information is available on neuropathogenesis of HIV-1 subtype C (clade C) that exists in Sub-Saharan Africa and Asia. Therefore, studies to identify specific neuropathogenic mechanisms associated with HAND are worth pursuing to dissect the mechanisms underlying this modulation and to prevent HAND particularly in clade B infection. In this study, the authors have investigated 84 key human synaptic plasticity genes differential expression profile in clade B and clade C infected primary human astrocytes by using RT(2) Profile PCR Array human Synaptic Plasticity kit. Among these, 31 and 21 synaptic genes were significantly (≥3 fold) down-regulated and 5 genes were significantly (≥3 fold) up-regulated in clade B and clade C infected cells, respectively compared to the uninfected control astrocytes. In flow-cytometry analysis, down-regulation of postsynaptic density and dendrite spine morphology regulatory proteins (ARC, NMDAR1 and GRM1) was confirmed in both clade B and C infected primary human astrocytes and SK-N-MC neuroblastoma cells. Further, spine density and dendrite morphology changes by confocal microscopic analysis indicates significantly decreased spine density, loss of spines and decreased dendrite diameter, total dendrite and spine area in clade B infected SK-N-MC neuroblastoma cells compared to uninfected and clade C infected cells. The authors have also observed that, in clade B infected astrocytes, induction of apoptosis was significantly higher than in the clade C infected astrocytes. In conclusion, this study suggests that down-regulation of synaptic plasticity genes, decreased dendritic spine density and induction of apoptosis in astrocytes may contribute to the severe neuropathogenesis in clade B infection.

What's God Got To Do With It? Engaging African-American Faith-Based Institutions In HIV Prevention. Nunn A, Cornwall A, Thomas G, Callahan PL, Waller PA, Friend R, Broadnax PJ, Flanigan T. Glob Public Health. 2013; 8(3): 258-269. doi: 10.1080/17441692.2012.759608. Epub 2013 Feb 4.

African-Americans are disproportionately infected and affected by HIV/AIDS. Although faith-based institutions play critical leadership roles in the African-American community, the faith-based response to HIV/AIDS has historically been lacking. The authors explore recent successful strategies of a citywide HIV/AIDS awareness and testing campaign developed in partnership with 40 African-American faith-based institutions in Philadelphia, Pennsylvania, a city with some of the USA's highest HIV infection rates. Drawing on important lessons from the campaign and subsequent efforts to sustain the campaign's momentum with a citywide HIV testing, treatment and awareness programme, the authors provide a road map for engaging African-American faith communities in HIV prevention that includes partnering with faith leaders, engaging the media to raise awareness, destigmatising HIV/AIDS and encouraging

HIV testing, and conducting educational and HIV testing events at houses of worship. African-American faith-based institutions have a critical role to play in raising awareness about the HIV/AIDS epidemic and reducing racial disparities in HIV infection.

Externally Controlled On-Demand Release Of Anti-HIV Drug Using Magneto-Electric Nanoparticles As Carriers. Nair M, Guduru R, Liang P, Hong J, Sagar V, Khizroev S. Nat Commun. 2013; 4: 1707. doi: 10.1038/ncomms2717.
Although highly active anti-retroviral therapy has resulted in remarkable decline in the morbidity and mortality in AIDS patients, inadequately low delivery of anti-retroviral drugs across the blood-brain barrier results in virus persistence. The capability of high-efficacy-targeted drug delivery and on-demand release remains a formidable task. Here the authors report an in vitro study to demonstrate the on-demand release of azidothymidine 5'-triphosphate, an anti-human immunodeficiency virus drug, from 30 nm CoFe2O4@BaTiO3 magneto-electric nanoparticles by applying a low alternating current magnetic field. Magneto-electric nanoparticles as field-controlled drug carriers offer a unique capability of field-triggered release after crossing the blood-brain barrier. Owing to the intrinsic magnetoelectricity, these nanoparticles can couple external magnetic fields with the electric forces in drug-carrier bonds to enable remotely controlled delivery without exploiting heat. Functional and structural integrity of the drug after the release was confirmed in in vitro experiments with human immunodeficiency virus-infected cells and through atomic force microscopy, spectrophotometry, Fourier transform infrared and mass spectrometry studies.

Development Of the Perceived Risk Of HIV Scale. Napper LE, Fisher DG, Reynolds GL. AIDS Behav. 2012 May; 16(4): 1075-1083. doi: 10.1007/s10461-011-0003-2.
Past studies have used various methods to assess perceived risk of HIV infection; however, few have included multiple items covering different dimensions of risk perception or have examined the characteristics of individual items. This study describes the use of Item Response Theory (IRT) to develop a short measure of perceived risk of HIV infection scale (PRHS). An item pool was administered by trained interviewers to 771 participants. Participants also completed the risk behavior assessment (RBA) which includes items measuring risky sexual behaviors, and 652 participants completed HIV testing. The final measure consisted of 8 items, including items assessing likelihood estimates, intuitive judgments and salience of risk. Higher scores on the PRHS were positively associated with a greater number of sex partners, episodes of unprotected sex and having sex while high. Participants who tested positive for HIV reported higher perceived risk. The PRHS demonstrated good reliability and concurrent criterion-related validity. Compared to single item measures of risk perception, the PRHS is more robust by examining multiple dimensions of perceived risk. Possible uses of the measure and directions for future research are discussed.

Rapid Progression To Decompensated Cirrhosis, Liver Transplant, and Death In HIV-Infected Men After Primary Hepatitis C Virus Infection. Fierer DS, Dieterich DT, Fiel MI, Branch AD, Marks KM, Fusco DN, Hsu R, Smith DM, Fierer J. Clin Infect Dis. 2013 Apr; 56(7): 1038-1043. doi: 10.1093/cid/cis1206.
The authors and others have shown that primary hepatitis C (HCV) infection in men infected with human immunodeficiency virus (HIV) causes early-onset liver fibrosis; however, little is known about the long-term natural history of the liver disease in these HIV-infected men. The

authors followed a cohort of HIV-infected men with primary HCV infection in New York City. Results showed that four men who were not cured after their primary HCV infection developed decompensated cirrhosis within 17 months to 6 years after primary HCV infection. Three died within 8 years of primary HCV infection, and 1 survived after liver transplant done 2 years after primary HCV infection. Three of the 4 men had AIDS at the time of primary HCV infection, and the most rapid progression occurred in the 2 men with the lowest CD4 counts at the time of HCV infection. Liver histopathology was most consistent with HCV-induced damage even though some had exposures to other potential hepatotoxins. The authors conclude that primary HCV infection resulted in decompensated cirrhosis and death within 2-8 years in 4 HIV-infected men. The rapid onset of fibrosis due to primary HCV infection in HIV-infected men cannot therefore be considered benign. The rate of continued progression to liver failure may be proportional to the degree of underlying immunocompromise caused by HIV infection. More research is needed to better define the mechanisms behind accelerated liver damage.

The Incidence and Prevalence Of Hepatitis C In Prisons and Other Closed Settings: Results Of A Systematic Review and Meta-Analysis. Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, Hagan H, Rich JD, van den Bergh BJ, Degenhardt L. Hepatology. 2013 Mar 15. doi: 10.1002/hep.26387.Epub ahead of print.

People detained in prisons and other closed settings are at elevated risk of infection with hepatitis C virus (HCV). The authors undertook a systematic review and meta-analysis with the aim of determining the rate of incident HCV infection and the prevalence of anti-HCV among detainees of closed settings. The authors systematically searched databases of peer-reviewed literature and widely distributed a call for unpublished data. They calculated summary estimates of incidence and prevalence among general population detainees and detainees with a history of injecting drug use (IDU), and explored heterogeneity through stratification and meta-regression. The summary prevalence estimates were used to estimate the number of anti-HCV positive prisoners globally. HCV incidence among general detainees was 1.4 per 100 person-years (py; 95% CI: 0.1, 2.7; k=4), and 16.4 per 100py (95% CI: 0.8, 32.1; k=3) among detainees with a history of IDU. The summary prevalence estimate of anti-HCV in general detainees was 26% (95% CI: 23%, 29%; k=93), and in detainees with a history of IDU, 64% (95% CI: 58%, 70%; k=51). The regions of highest prevalence were Central Asia (38%; 95% CI 32%, 43%; k=1) and Australasia (35%; 95% CI: 28%, 43%; k=9). The authors estimate that 2.2 million (range: 1.4 million – 2.9 million) detainees globally are anti-HCV positive, with the largest populations in North America (668,500; range: 553,500-784,000) and East and Southeast Asia (638,000; range: 332,000-970,000). The authors conclude that HCV is a significant concern in detained populations, with one in four detainees anti-HCV positive. Epidemiological data on the extent of HCV infection in detained populations is lacking in many countries. Greater attention towards prevention, diagnosis and treatment of HCV infection among detained populations is urgently required.

Mechanism Of Autoinduction Of Methadone N-Demethylation In Human Hepatocytes. Campbell SD, Crafford A, Williamson BL, Kharasch ED. Anesth Analg. 2013 Jul; 117(1): 52-60. doi: 10.1213/ANE.0b013e3182918252. Epub 2013 Jun 3.

There is considerable interindividual and intraindividual variability in methadone metabolism and clearance. Methadone dosing is particularly challenging during initiation of therapy,

because of time-dependent increases in hepatic clearance (autoinduction). Although methadone N-demethylation is catalyzed in vitro by cytochrome P4502B6 (CYP2B6) and CYP3A4, and clearance in vivo depends on CYP2B6, mechanism(s) of autoinduction are incompletely understood. In this investigation, the authors determined mechanism(s) of methadone autoinduction using human hepatocytes. Fresh human hepatocytes were exposed to 0.1 to 10 µM methadone for 72 hours. Cells were washed and methadone N-demethylation assessed. CYP2B6, CYP3A4, and CYP3A5 messenger RNA (mRNA), protein expression (by gel-free high-performance liquid chromatography mass spectrometry) and catalytic activity (bupropion hydroxylation and alfentanil dealkylation for CYP2B6 and CYP3A4/5, respectively) were measured. Mechanisms of CYP induction were characterized using pregnane X receptor and constitutive androstane receptor reporter gene assays. Methadone (10 µM) increased methadone N-demethylation 2-fold, CYP2B6 and CYP3A4 mRNA 3-fold, and protein expression 2-fold. CYP3A5 mRNA was unchanged. CYP2B6 and CYP3A4/5 activities increased 2-fold. Induction by methadone enantiomers (R-methadone versus S-methadone) did not differ. Induction was relatively weak compared with maximum induction by phenobarbital and rifampin. Lower methadone concentrations had smaller effects. Methadone was an agonist for the pregnane X receptor but not the constitutive androstane receptor. The authors conclude that methadone caused concentration-dependent autoinduction of methadone N-demethylation in human hepatocytes, related to induction of CYP2B6 and CYP3A4 mRNA expression, protein expression, and catalytic activity. Induction was related to pregnane X receptor but not constitutive androstane receptor activation. These in vitro findings provide mechanistic insights into clinical autoinduction of methadone metabolism and clearance.

Maintenance Of Th1 HCV-Specific Responses In Individuals With Acute HCV Who Achieve Sustained Virological Clearance After Treatment. Flynn JK, Dore GJ, Hellard M, Yeung B, Rawlinson WD, White PA, Kaldor JM, Lloyd AR, French RA; ATAHC Study Group. J Gastroenterol Hepatol. 2013 May 10. doi: 10.1111/jgh.12265. [Epub ahead of print]. T cell responses against hepatitis C are believed to be critical in achieving both natural and treatment induced clearance. However, rapid clearance of antigen with early treatment of primary infection may result in reduced or poorly sustained cellular immunity. This study longitudinally examined Th1 and Th2 HCV-specific cytokine production and T cell effector function from subjects enrolled in the Australian Trial in Acute Hepatitis C (ATAHC) comparing three groups: treatment-induced clearance (sustained virological response [SVR]), treatment non-response, and untreated spontaneous clearance. HCV-specific T cell responses were characterized by HCV peptide ELISpot, in-vitro cytokine production and T cell flow cytometry assays. Treated subjects with a SVR displayed a better maintenance of HCV-specific Th1 responses compared to treatment non-responders (higher interferon (IFN)-γ and interleukin (IL)-2 magnitude week 24, broader IFN-γ responses week 24 and 48, $p<0.05$), and significantly increased IFN-γ responses between screening and week 48 (magnitude $p=0.026$, breadth $p=0.009$). Treatment-induced viral clearance was also associated with a trend towards decreased IL-10 responses (screening to week 48 $p=0.070$), higher expression of CD45RO ($p=0.042$) and CD38 ($p=0.088$) on $CD4^+$ T cells and higher IFN-γR expression ($CD56^+$ IFN-γR^+ $p=0.033$) compared to treatment non-responders. Untreated subjects with viral clearance also displayed high magnitude and broad HCV-specific IFN-γ and IL-2 responses early in infection, however IFN-γ responses were not as well maintained compared to treated subjects

with a SVR (week 48 magnitude, breadth p=0.064). The authors conclude that treatment-induced viral clearance of recent HCV infection is associated with maintenance of HCV-specific Th1 responses.

Plasma Interferon-Gamma-Inducible Protein-10 (IP-10) Levels During Acute Hepatitis C Virus Infection. Grebely J, Feld JJ, Applegate T, Matthews GV, Hellard M, Sherker A, Petoumenos K, Zang G, Shaw I, Yeung B, George J, Teutsch S, Kaldor JM, Cherepanov V, Bruneau J, Shoukry NH, Lloyd AR, Dore GJ. Hepatology. 2013 Jun; 57(6): 2124-2134. doi: 10.1002/hep.26263. Epub 2013 May 8.

Systemic levels of interferon-gamma-inducible protein-10 (IP-10) are predictive of treatment-induced clearance in chronic hepatitis C virus (HCV). In the present study, factors associated with plasma IP-10 levels at the time of acute HCV detection and the association between IP-10 levels and spontaneous clearance were assessed in three cohorts of acute HCV infection. Among 299 individuals, 245 (181 male, 47 human immunodeficiency virus-positive [HIV+]) were HCV RNA+ at acute HCV detection. In adjusted analysis, factors independently associated with IP-10 levels ≥150 pg/mL (median level) included HCV RNA levels >6 log IU/mL, HIV coinfection and non-Aboriginal ethnicity. Among 245 HCV RNA+ at acute HCV detection, 214 were untreated (n = 137) or had persistent infection (infection duration ≥26 weeks) at treatment initiation (n = 77). Spontaneous clearance occurred in 14% (29 of 214). Individuals without spontaneous clearance had significantly higher mean plasma IP-10 levels at the time of acute HCV detection than those with clearance (248 ± 32 versus 142 ± 22 pg/mL, P = 0.008). The proportion of individuals with spontaneous clearance was 0% (0 of 22, P = 0.048) and 16% (27 of 165) and in those with and without plasma IP-10 levels ≥380 pg/mL. In adjusted analyses, favorable IL28B genotype was associated with spontaneous clearance, while higher HCV RNA level was independently associated with lower odds of spontaneous clearance. High IP-10 levels at acute HCV detection were associated with failure to spontaneously clear HCV. Patients with acute HCV and high baseline IP-10 levels, particularly >380 pg/mL, should be considered for early therapeutic intervention, and those with low levels should defer therapy for potential spontaneous clearance.

Faldaprevir Combined With Pegylated Interferon Alfa-2a and Ribavirin In Treatment-Naïve Patients With Chronic Genotype1 HCV: SILEN-C1 Trial. Sulkowski MS, Bourlière M, Bronowicki JP, Asselah T, Pawlotsky JM, Shafran SD, Pol S, Mauss S, Larrey D, Datsenko Y, Stern JO, Kukolj G, Scherer J, Nehmiz G, Steinmann GG, Böcher WO. Hepatology. 2013 Jun; 57(6): 2155-2163. doi: 10.1002/hep.26386.

Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor with pharmacokinetic properties supportive of once-daily (QD) dosing. Four hundred and twenty-nine HCV genotype (GT)-1 treatment-naïve patients without cirrhosis were randomized 1:1:2:2 to receive 24 weeks of pegylated interferon alfa-2a and ribavirin (PegIFN/RBV) in combination with placebo, faldaprevir 120 mg QD with 3 days of PegIFN/RBV lead-in (LI), 240 mg QD with LI, or 240 mg QD without LI, followed by an additional 24 weeks of PegIFN/RBV. Patients in the 240 mg QD groups achieving maintained rapid virologic response (mRVR; viral load [VL] <25 IU/mL at week 4 and undetectable at weeks 8-20) were rerandomized to cease all treatment at week 24 or continue receiving PegIFN/RBV up to week 48. VL was measured by Roche TaqMan. Sustained virologic response (SVR) rates were 56%, 72%, 72%, and 84% in the placebo, faldaprevir 120 mg QD/LI, 240 mg QD/LI, and 240 mg

QD groups. Ninety-two percent of mRVR patients treated with faldaprevir 240 mg QD achieved SVR, irrespective of PegIFN/RBV treatment duration. Eighty-two percent of GT-1a patients who received faldaprevir 240 mg QD achieved SVR versus 47% with placebo. Mild gastrointestinal disorders, jaundice resulting from isolated unconjugated hyperbilirubinemia, and rash or photosensitivity were more common in the active groups than with placebo. Discontinuations resulting from adverse events occurred in 4%, 11%, and 5% of patients treated with 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD of faldaprevir versus 1% with placebo. The authors conclude that Faldaprevir QD with PegIFN/RBV achieved consistently high SVR rates with acceptable tolerability and safety at all dose levels. The 120 and 240 mg QD doses are currently undergoing phase 3 evaluation.

ITX 5061 Quantitation In Human Plasma With Reverse Phase Liquid Chromatography and Mass Spectrometry Detection. Hochreiter J, Lapham J, Wong-Staal F, McKelvy J, Sulkowski M, Glesby MJ, Johnson VA, Morse GD. Antivir Ther. 2013; 18(3): 329-336. doi: 10.3851/IMP2354. Epub 2012 Sep 6.

ITX 5061 is a highly potent small molecule inhibitor of scavenger receptor-B1, an integral transmembrane protein that is found in liver cells and is actively involved in the transport of HCV into hepatocytes. Currently, ITX 5061 is being investigated in monoinfected hepatitis C patients in a proof-of-concept clinical trial carried out by the AIDS Clinical Trial Group (ACTG). To provide quantitative results in human plasma for pharmacokinetic analysis, an assay for ITX 5061 was validated. ITX 5061 and the internal standard, a deuterated analogue, were separated by isocratic reverse phase chromatography using a Polar RP column (Phenomenex Synergi(™); 2.0 mm × 50 mm, 4 μm) and detected via electrospray coupled to a triple quadrupole mass spectrometer with a run time of 5 min. Multiple reaction monitoring in positive mode was used with ITX 5061 at 585/114 m/z and the internal standard at 592/122 m/z with a linear range of 2.50-5,000 ng/ml. Human plasma was extracted using a protein precipitation combing 400 μl of acetonitrile with 100 μl of EDTA plasma. The interassay variation ranged from 1.19 to 13.2%, while the intraassay variation ranged from 0.394 to 12.9% over 6 days of testing. The method was successfully applied to the samples collected for the ACTG Protocol A5277. Plasma concentrations at 1 h and 24 h following 150 mg ITX 5061 daily in HCV monoinfected patients (n=3) ranged from 138 to 518 ng/ml and 33 to 111 ng/ml, respectively. The authors conclude that the ITX 5061 assay is accurate and reproducible with a wide linear range and will be used for pharmacokinetic analysis and dose-finding studies in HCV-monoinfected patients.

Targeted Brain Derived Neurotropic Factors (BDNF) Delivery Across the Blood-Brain Barrier For Neuro-Protection Using Magnetic Nano Carriers: An In-Vitro Study. Pilakka-Kanthikeel S, Atluri VS, Sagar V, Saxena SK, Nair M. PLoS One. 2013 Apr 30; 8(4): e62241. doi: 10.1371/journal.pone.0062241.

Parenteral use of drugs; such as opiates exert immunomodulatory effects and serve as a cofactor in the progression of HIV-1 infection, thereby potentiating HIV related neurotoxicity ultimately leading to progression of NeuroAIDS. Morphine exposure is known to induce apoptosis, down regulate cAMP response element-binding (CREB) expression and decrease in dendritic branching and spine density in cultured cells. Use of the neuroprotective agent, brain derived neurotropic factor (BDNF), which protects neurons against these effects, could be of therapeutic benefit in the treatment of opiate addiction. Previous studies have shown that

BDNF was not transported through the blood brain barrier (BBB) in-vivo, and hence it is not effective in-vivo. Therefore, development of a drug delivery system that can cross BBB may have significant therapeutic advantage. In the present study, the authors hypothesized that a magnetically guided nanocarrier may provide a viable approach for targeting BDNF across the BBB. They developed a magnetic nanoparticle (MNP) based carrier bound to BDNF and evaluated its efficacy and ability to transmigrate across the BBB using an in-vitro BBB model. The end point determinations of BDNF that crossed BBB were apoptosis, CREB expression and dendritic spine density measurement. The authors found that transmigrated BDNF was effective in suppressing the morphine induced apoptosis, inducing CREB expression and restoring the spine density. Their results suggest that the developed nanocarrier will provide a potential therapeutic approach to treat opiate addiction, protect neurotoxicity and synaptic density degeneration.

Hypocretin/Orexin Neurons Contribute To Hippocampus-Dependent Social Memory and Synaptic Plasticity In Mice. Yang L, Zou B, Xiong X, Pascual C, Xie J, Malik A, Xie J, Sakurai T, Xie XS. J Neurosci. 2013 Mar 20; 33(12): 5275-5284. doi: 10.1523/JNEUROSCI.3200-12.2013. Drug Alcohol Depend. 2013 Jun 1; 130(1-3): 208-214. doi: 10.1016/j.drugalcdep.2012.11.008. Hypocretin/orexin (Hcrt)-producing neurons in the lateral hypothalamus project throughout the brain, including to the hippocampus, where Hcrt receptors are widely expressed. Hcrt neurons activate these targets to orchestrate global arousal state, wake-sleep architecture, energy homeostasis, stress adaptation, and reward behaviors. Recently, Hcrt has been implicated in cognitive functions and social interaction. In the present study, the authors tested the hypothesis that Hcrt neurons are critical to social interaction, particularly social memory, using neurobehavioral assessment and electrophysiological approaches. The validated "two-enclosure homecage test" devices and procedure were used to test sociability, preference for social novelty (social novelty), and recognition memory. A conventional direct contact social test was conducted to corroborate the findings. The authors found that adult orexin/ataxin-3-transgenic (AT) mice, in which Hcrt neurons degenerate by 3 months of age, displayed normal sociability and social novelty with respect to their wild-type littermates. However, AT mice displayed deficits in long-term social memory. Nasal administration of exogenous Hcrt-1 restored social memory to an extent in AT mice. Hippocampal slices taken from AT mice exhibited decreases in degree of paired-pulse facilitation and magnitude of long-term potentiation, despite displaying normal basal synaptic neurotransmission in the CA1 area compared to wild-type hippocampal slices. AT hippocampi had lower levels of phosphorylated cAMP response element-binding protein (pCREB), an activity-dependent transcription factor important for synaptic plasticity and long-term memory storage. These studies demonstrate that Hcrt neurons play an important role in the consolidation of social recognition memory, at least in part through enhancements of hippocampal synaptic plasticity and cAMP response element-binding protein phosphorylation.

Cognitive Deficits In Long-Term Anabolic-Androgenic Steroid Users. Kanayama G, Kean J, Hudson JI, Pope HG Jr. Drug Alcohol Depend. 2013 Jun 1; 130(1-3): 208-214. doi: 10.1016/j.drugalcdep.2012.11.008.
Millions of individuals worldwide have used anabolic-androgenic steroids (AAS) to gain muscle or improve athletic performance. Recently, in vitro investigations have suggested that supraphysiologic AAS doses cause apoptosis of neuronal cells. These findings raise the

possibility, apparently still untested, that humans using high-dose AAS might eventually develop cognitive deficits. The authors administered five cognitive tests from the computerized CANTAB battery (Pattern Recognition Memory, Verbal Recognition Memory, Paired Associates Learning, Choice Reaction Time, and Rapid Visual Information Processing) to 31 male AAS users and 13 non-AAS-using weightlifters age 29-55, recruited and studied in May 2012 in Middlesbrough, UK. Testers were blinded to participants' AAS status and other historical data. Long-term AAS users showed no significant differences from nonusers on measures of response speed, sustained attention, and verbal memory. On visuospatial memory, however, AAS users performed significantly more poorly than nonusers, and within the user group, visuospatial performance showed a significant negative correlation with total lifetime AAS dose. These were large effects: on Pattern Recognition Memory, long-term AAS users underperformed nonusers by almost one standard deviation, based on normative population scores (adjusted mean difference in z-scores=0.89; p=0.036), and performance on this test declined markedly with increasing lifetime AAS dose (adjusted change in z-score=-0.13 per 100g of lifetime AAS dose; p=0.002). These results remained stable in sensitivity analyses addressing potential confounding factors. These preliminary findings raise the ominous possibility that long-term high-dose AAS exposure may cause cognitive deficits, notably in visuospatial memory.

Regulation Of Cytochrome P450 2e1 Expression By Ethanol: Role Of Oxidative Stress-Mediated Pkc/Jnk/Sp1 Pathway. Jin M, Ande A, Kumar A, Kumar S. Cell Death Dis. 2013 Mar 21; 4: e554. doi: 10.1038/cddis.2013.78.

CYP2E1 metabolizes ethanol leading to production of reactive oxygen species (ROS) and acetaldehyde, which are known to cause not only liver damage but also toxicity to other organs. However, the signaling pathways involved in CYP2E1 regulation by ethanol are not clear, especially in extra-hepatic cells. This study was designed to examine the role of CYP2E1 in ethanol-mediated oxidative stress and cytotoxicity, as well as signaling pathways by which ethanol regulates CYP2E1 in extra-hepatic cells. In this study, the authors used astrocytic and monocytic cell lines, because they are important cells in central nervous system. Their results showed that 100 mM ethanol significantly induced oxidative stress, apoptosis, and cell death at 24 h in the SVGA astrocytic cell line, which was rescued by a CYP2E1 selective inhibitor, diallyl sulfide (DAS), CYP2E1 siRNA, and antioxidants (vitamins C and E). Further, the authors showed that DAS and vitamin C abrogated ethanol-mediated (50 mM) induction of CYP2E1 at 6 h, as well as production of ROS at 2 h, suggesting the role of oxidative stress in ethanol-mediated induction of CYP2E1. The authors then investigated the role of the protein kinase C/c-Jun N-terminal kinase/specificity protein1 (PKC/JNK/SP1) pathway in oxidative stress-mediated CYP2E1 induction. Their results showed that staurosporine, a non-specific inhibitor of PKC, as well as specific PKCζ inhibitor and PKCζ siRNA, abolished ethanol-induced CYP2E1 expression. In addition, inhibitors of JNK (SP600125) and SP1 (mithramycin A) completely abrogated induction of CYP2E1 by ethanol in SVGA astrocytes. Subsequently, the authors showed that CYP2E1 is also responsible for ethanol-mediated oxidative stress and apoptotic cell death in U937 monocytic cell lines. Finally, their results showed that PKC/JNK/SP1 pathway is also involved in regulation of CYP2E1 in U937 cells. This study has clinical implications with respect to alcohol-associated neuroinflammatory toxicity among alcohol users.

SERVICES RESEARCH

Missed Opportunities for Hepatitis C Testing in Opioid Treatment Programs. Crimping JA. Am J Public Health. 2013; Epub ahead of print.
HCV has surpassed HIV as a cause of death in the United States and is particularly prevalent among injection drug users. This study examined the availability of on-site HCV testing in a nationally representative sample of opioid treatment programs. Nearly 68% of these programs had the staff required for HCV testing, but only 34% offered on-site testing. Availability of on-site testing increased only slightly with the proportion of injection drug users among clients. The limited HCV testing services in opioid treatment programs is a key challenge to reducing HCV in the US population.

Mapping Common Psychiatric Disorders: Structure and Predictive Validity in The National Epidemiologic Survey on Alcohol and Related Conditions. Blanco C, Krueger R, Hasin D, Liu S, Wang S, Kerridge B, Saha T, Olfson M. JAMA Psychiatry. 2013; 70(2): 199-208.
Clinical experience and factor analytic studies suggest that some psychiatric disorders may be more closely related to one another, as indicated by the frequency of their co-occurrence, which may have etiologic and treatment implications. The objective of this study was to construct a virtual space of common psychiatric disorders, spanned by factors reflecting major psychopathologic dimensions, and locate psychiatric disorders in that space, as well as to examine whether the location of disorders at baseline predicts the prevalence and incidence of disorders at 3-year follow-up. A total of 34,653 individuals participated in waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. Main outcome measures comprised the distance between disorders at wave 1, calculated using the loadings of the factors spanning the space of disorders as coordinates. This distance was correlated with the adjusted odds ratios for age, sex, and race/ethnicity of the prevalence and incidence of Axis I disorders in wave 2, with the aim of determining whether smaller distances between disorders at wave 1 predicts higher disorder prevalence and incidence at wave 2. A model with 3 correlated factors provided an excellent fit (Comparative Fit Index = 0.99, Tucker-Lewis Index = 0.98, root mean square error of approximation = 0.008) for the structure of common psychiatric disorders and was used to span the space of disorders. Distances ranged from 0.070 (between drug abuse and alcohol dependence) to 1.032 (between drug abuse and dysthymia). The correlation of distance between disorders in wave 1 with adjusted odds ratios of prevalence in wave 2 was -0.56. The correlation of distance in wave 1 with adjusted odds ratios of incidence in wave 2 was -0.57. The authors conclude that mapping psychiatric disorders can be used to quantify the distances among disorders. Proximity in turn can be used to predict prospectively the incidence and prevalence of Axis I disorders.

Disparities in Access to Physicians and Medications for the Treatment of Substance Use Disorders between Publicly and Privately Funded Treatment Programs in the United States. Abraham A, Knudsen H, Rieckmann T, Roman P. J Stud Alcohol Drugs. 2013; 74(2): 258-265.
Prior research suggests that publicly funded substance use disorder (SUD) treatment programs lag behind privately funded programs in adoption of evidence-based practices, resulting in disparities in access to high-quality SUD treatment. These disparities highlight a critical public

health concern because the majority of SUD patients in the United States are treated in the publicly funded treatment sector. This study uses recent data to examine disparities in access to physicians and availability of medications for the treatment of SUDs between publicly and privately funded SUD treatment programs. Data were collected from 595 specialty SUD treatment programs from 2007 to 2010 via face-to-face interviews, mailed surveys, and telephone interviews with treatment program administrators. Publicly funded programs were less likely than privately funded programs to have a physician on staff, even after controlling for several organizational characteristics that were associated with access to physicians. The results of negative binomial regression indicated that, even after taking into account physician access and other organizational variables, publicly funded programs prescribed fewer SUD medications than privately funded SUD treatment programs. The authors conclude that patients seeking treatment in publicly funded treatment programs continue to face disparities in access to high-quality SUD treatment that supports patients' choices among a range of medication options. However, implementation of the Affordable Care Act may facilitate greater access to physicians and use of medications in publicly funded SUD treatment programs.

Characteristics of Adults with Substance Use Disorders Expected to Be Eligible for Medicaid under the ACA. Busch S, Meara E, Huskamp H, Barry C. Psychiatr Serv. 2013: 1-7.

Provisions in the Affordable Care Act (ACA) are likely to expand access to substance use disorder treatment for low-income individuals. The aim of the study was to provide information on the need for substance use disorder treatment among individuals who may be eligible for Medicaid under the ACA. The 2008 and 2009 National Survey on Drug Use and Health provided data on demographic characteristics, health status, and substance use disorders for comparison of current low-income Medicaid enrollees (N=3,809) with currently uninsured individuals with household incomes that may qualify them for Medicaid coverage beginning in 2014 (N=5,049). The incomes of the groups compared were 138% of the federal poverty level (133% provided in the ACA plus a 5% income "disregard" allowed by the law). The rate of substance use disorders among currently uninsured income-eligible individuals was slightly higher than the rate among current Medicaid enrollees (14.6% versus 11.5%, p=.03). Although both groups had significant unmet need for substance use disorder treatment, the treatment rate among those who needed treatment was significantly lower in the income-eligible group than in the currently enrolled group (31.3% versus 46.8%, p<.01). When the analysis excluded informal care received outside the medical sector, treatment rates among those with treatment needs were much lower in both groups (12.8% in the income-eligible group and 30.7% among current enrollees). Findings suggest that Medicaid insurance expansions under the ACA will reduce unmet need for substance use disorder treatment.

Parity and Out-Of-Pocket Spending for Children with High Mental Health or Substance Abuse Expenditures. Barry C, Chien A, Normand S, Busch A, Azzone V, Goldman H, Huskamp H. Pediatrics. 2013; 131(3): e903-e911.

The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act required health plans to provide mental health and substance use disorder (MH/SUD) benefits on par with medical benefits beginning in 2010. Previous research found that parity significantly lowered average out-of-pocket (OOP) spending on MH/SUD treatment of

children. No evidence is available on how parity affects OOP spending by families of children with the highest MH/SUD treatment expenditures. The authors used a difference-in-differences study design to examine whether parity reduced families' (1) share of total MH/SUD treatment expenditures paid OOP or (2) average OOP spending among children whose total MH/SUD expenditures met or exceeded the 90th percentile. By using claims data, the authors compared changes 2 years before (1999-2000) and 2 years after (2001-2002) the Federal Employees Health Benefits Program implemented parity to a contemporaneous group of health plans that did not implement parity over the same 4-year period. The authors examined those enrolled in the Federal Employees Health Benefits Program because their parity directive is similar to and served as a model for the new federal parity law. Parity led to statistically significant annual declines in the share of total MH/SUD treatment expenditures paid OOP (-5%, 95% confidence interval: -6% to -4%) and average OOP spending on MH/SUD treatment (-$178, 95% confidence interval: -257 to -97). This study provides the first empirical evidence that parity reduces the share and level of OOP spending by families of children with the highest MH/SUD treatment expenditures; however, these spending reductions were smaller than anticipated and unlikely to meaningfully improve families' financial protection.

Impact of New Therapeutics for Hepatitis C Virus Infection in Incarcerated Populations.
Spaulding A, Kim A, Harzke A, Sullivan J, Linas B, Brewer A, Dickert J, McGovern B, Strick L, Trestman R, Ferguson W. Top Antivir Med. 2013; 21(1): 27-35.
Inmate populations bear a disproportionate share of the burden of hepatitis C virus (HCV) infection. With more than 90% of prisoners released back to their communities within a few years of sentencing, incarceration can be viewed as an opportunity to provide HCV screening and therapeutic interventions to benefit the individual, reduce the costs of HCV management to the health care system from a societal perspective, and improve overall public health. Although optimal medical management of HCV within prison settings would increase the current cost of correctional health care, it could decrease transmission within the community, reduce overall disease burden, and lower the future societal health care costs associated with end-stage liver disease. Nonetheless, most prison systems treat only a small fraction of infected inmates. Current and emerging therapeutic agents will cure HCV infection in the vast majority of patients. Mathematical modeling also shows that expanded HCV screening and treatment are cost-effective from the societal perspective. In this article, the authors describe appropriate treatment regimens, propose strategies to lessen the burden of these costly HCV therapies on correctional health care systems, and address the challenges of expanded HCV screening in correctional settings.

Contribution of Substance Use Disorders on HIV Treatment Outcomes and Antiretroviral Medication Adherence Among HIV-Infected Persons Entering Jail.
Chitsaz E, Meyer J, Krishnan A, Springer S, Marcus R, Zaller N, Jordan A, Lincoln T, Flanigan T, Porterfield J, Altice F. AIDS Behav. 2013: 1-9.
HIV and substance use are inextricably intertwined. One-sixth of people living with HIV/AIDS (PLWHA) transition through the correctional system annually. There is paucity of evidence on the impact of substance use disorders on HIV treatment engagement among jail detainees. The authors examined correlates of HIV treatment in the largest sample of PLWHA transitioning through jail in 10 US sites from 2007 to 2011. Cocaine, alcohol, cannabis, and

heroin were the most commonly used substances. Drug use severity was negatively and independently correlated with three outcomes just before incarceration: (1) having an HIV care provider (AOR = 0.28; 95 % CI 0.09-0.89); (2) being prescribed antiretroviral therapy (AOR = 0.12; 95 % CI 0.04-0.35) and (3) high levels (>95 %) of antiretroviral medication adherence (AOR = 0.18; 95 % CI 0.05-0.62). Demographic, medical and psychiatric comorbidity and social factors also contributed to poor outcomes. Evidence-based drug treatments that include multi-faceted interventions, including medication-assisted therapies, are urgently needed to effectively engage this vulnerable population.

Initiation of Buprenorphine during Incarceration and Retention in Treatment upon Release. Zaller N, McKenzie M, Friedmann PD, Green TC, McGowan S, Rich JD. J Subst Abuse Treat. 2013.

The authors report here on a feasibility study of initiating buprenorphine/naloxone prior to release from incarceration and linking participants to community treatment providers upon release. The study consisted of a small number of Rhode Island (RI) prisoners (N=44) diagnosed with opioid dependence. The study design is a single arm, open-label pilot study with a 6-month follow up interview conducted in the community. However, a natural experiment arose during the study comparing pre-release initiation of buprenorphine/naloxone to initiation post-release. Time to post-release prescriber appointment (mean days) for initiation of treatment outside Rhode Island Department of Corrections (RIDOC) versus inside RIDOC was 8.8 and 3.9, respectively (p=.1). Median post release treatment duration (weeks) for outside RIDOC versus inside RIDOC was 9 and 24, respectively (p=.007). The authors conclude that initiating buprenorphine/naloxone prior to release from incarceration may increase engagement and retention in community-based treatment.

Forced Withdrawal from Methadone Maintenance Therapy in Criminal Justice Settings: A Critical Treatment Barrier in the United States. Fu J, Zaller N, Yokell M, Bazazi A, Rich J. J Subst Abuse Treat. 2013; 44(5): 502-505.

The World Health Organization classifies methadone as an essential medicine, yet methadone maintenance therapy remains widely unavailable in criminal justice settings throughout the United States. Methadone maintenance therapy is often terminated at the time of incarceration, with inmates forced to withdraw from this evidence-based therapy. The authors assessed whether these forced withdrawal policies deter opioid-dependent individuals in the community from engaging methadone maintenance therapy in two states that routinely force inmates to withdraw from methadone (N = 205). Nearly half of all participants reported that concern regarding forced methadone withdrawal during incarceration deterred them from engaging in methadone maintenance therapy in the community. Participants in the state where more severe methadone withdrawal procedures are used during incarceration were more likely to report concern regarding forced withdrawal as a treatment deterrent. Methadone withdrawal policies in the criminal justice system may be a broader treatment deterrent for opioid-dependent individuals than previously realized. Redressing this treatment barrier is both a health and human rights imperative.

Patterns of Homelessness and Implications for HIV Health after Release from Jail.
Zelenev A, Marcus R, Kopelev A, Cruzado-Quinones J, Spaulding A, Desabrais M, Lincoln T, Altice F. AIDS Behav. 2013: 1-14.
This empirical study examines the association between substance abuse, mental illness, health behaviors and different patterns of homelessness among recently released, HIV-infected jail detainees. Using longitudinal data from a 10-site study, the authors examine correlates of homelessness, transitions to and from stable housing and the effect of housing on HIV treatment outcomes. Based on their analysis, they found evidence that the transitions from homelessness are closely associated with a reduction in the use of alcohol and illicit drugs, a decline in drug addiction severity, and an improvement in mental health. In addition, the authors found evidence that disparities in the housing status contributed substantially to the observed gap in the HIV treatment outcomes between homeless and non-homeless patients, including in achievement of virological suppression over time.

Frequent Emergency Department Use among Released Prisoners with Human Immunodeficiency Virus: Characterization Including a Novel Multi-morbidity Index.
Meyer J, Qiu J, Chen N, Larkin G, Altice F. Acad Emerg Med. 2013; 20(1): 79-88.
The objective of this study was to characterize the medical, social, and psychiatric correlates of frequent emergency department (ED) use among released prisoners with human immunodeficiency virus (HIV). Data on all ED visits by 151 released prisoners with HIV on antiretroviral therapy (ART) were prospectively collected for 12 months. Correlates of frequent ED use, defined as having two or more ED visits post release, were described using univariate and multivariate models and generated medical, psychiatric, and social multi-morbidity indices. Forty-four (29%) of the 151 participants were defined as frequent ED users, accounting for 81% of the 227 ED visits. Frequent ED users were more likely than infrequent or nonusers to be female; have chronic medical illnesses that included seizures, asthma, and migraines; and have worse physical health-related quality of life (HRQoL). In multivariate Poisson regression models, frequent ED use was associated with lower physical HRQoL (odds ratio [OR] = 0.95, p = 0.02) and having not had prerelease discharge planning (OR = 3.16, p = 0.04). Frequent ED use was positively correlated with increasing psychiatric multi-morbidity index values. Among released prisoners with HIV, frequent ED use is driven primarily by extensive comorbid medical and psychiatric illness. Frequent ED users were also less likely to have received prerelease discharge planning, suggesting missed opportunities for seamless linkages to care.

Improvements in Methadone Treatment Outcomes for Probationers/Parolees Regardless of Early Counseling. Kelly S, O'Grady K, Jaffe J, Gandhi D, Schwartz R. J Addict Med. 2013; 7(2): 133-138.
This secondary data analysis examined the association between criminal justice (CJ) status and outcomes over 12 months of methadone maintenance treatment. 230 newly admitted patients were randomly assigned to methadone either with or without counseling for 4 months followed by standard methadone treatment with counseling. Participants completed the ASI and urine drug testing at baseline and 4- and 12-month follow-up and the Treatment Readiness (TR) scale at baseline. The relationship between baseline CJ status (whether participants were on probation or parole), CJ status by study counseling condition, and CJ status by TR with heroin and cocaine use, illegal activity, days in treatment and treatment retention, arrests, and the

number of days incarcerated or hospitalized during follow-up was examined. Compared with participants not on probation/parole, probationers/parolees showed significant reductions in cocaine-positive tests from baseline to 12 months ($P < 0.001$). Probationers/parolees additionally reported significantly fewer days of illegal activity than non-probationers/parolees at 12 months ($P = 0.02$). There was no relationship between CJ status and counseling condition for any outcomes. The relationship between CJ status and TR was significant only for cocaine-positive tests assessed over time ($P = 0.017$). Findings suggest that methadone participants on probation/parole showed improvements in outcomes in comparison with participants not on probation/parole, regardless of whether they received counseling during the first 4 months of treatment.

Characterizing Durations of Heroin Abstinence in the California Civil Addict Program: Results from a 33-Year Observational Cohort Study. Nosyk B, Anglin MD, Brecht M-L, Lima VD, Hser Y-I. Am J Epidemiol. 2013; 177(7): 675-682.
In accordance with the chronic disease model of opioid dependence, cessation is often observed as a longitudinal process rather than a discrete endpoint. The authors aimed to characterize and identify predictors of periods of heroin abstinence in the natural history of recovery from opioid dependence. Data were collected on participants from California who were enrolled in the Civil Addict Program from 1962 onward by use of a natural history interview. Multivariate regression using proportional hazards frailty models was applied to identify independent predictors and correlates of repeated abstinence episode durations. Among 471 heroin-dependent males, 387 (82.2%) reported 932 abstinence episodes, 60.3% of which lasted at least 1 year. Multivariate analysis revealed several important findings. First, demographic factors such as age and ethnicity did not explain variation in durations of abstinence episodes. However, employment and lower drug use severity predicted longer episodes. Second, abstinence durations were longer following sustained treatment versus incarceration. Third, individuals with multiple abstinence episodes remained abstinent for longer durations in successive episodes. Finally, abstinence episodes initiated >10 and ≤20 years after first use lasted longer than others. Public policy facilitating engagement of opioid-dependent individuals in maintenance-oriented drug treatment and employment is recommended to achieve and sustain opioid abstinence.

Opioid Agonist Treatments and Heroin Overdose Deaths in Baltimore, Maryland, 1995-2009. Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, Olsen Y, Mitchell SG, Jaffe JH. Am J Public Health. 2013; e-pub ahead of print.
The researchers examined the association between the expansion of methadone and buprenorphine treatment and the prevalence of heroin overdose deaths in Baltimore, Maryland from 1995 to 2009. A longitudinal time series analysis of archival data was conducted using linear regression with the Newey-West method to correct SEs for heteroscedasticity and autocorrelation, adjusting for average heroin purity. Overdose deaths attributed to heroin ranged from a high of 312 in 1999 to a low of 106 in 2008. While mean heroin purity rose sharply (1995-1999), the increasing number of patients treated with methadone was not associated with a change in the number of overdose deaths, but starting in 2000 expansion of opioid agonist treatment was associated with a decline in overdose deaths. Adjusting for heroin purity and the number of methadone patients, there was a statistically significant inverse relationship between heroin overdose deaths and patients treated with buprenorphine

(P = .002). Increased access to opioid agonist treatment was associated with a reduction in heroin overdose deaths. Implementing policies that support evidence-based medication treatment of opiate dependence may decrease heroin overdose deaths.

Client Incentives Versus Contracting and Staff Incentives: How Care Continuity Interventions in Substance Abuse Treatment Can Improve Residential to Outpatient Transition. Acquavita S, Stershic S, Sharma R, Stitzer M. J Subst Abuse Treat. 2013; 45(1): 55-62.
Interventions for improving transition from short-term residential to outpatient treatment were examined. Usual care (UC; n=114) was referral to a preferred outpatient program with advance appointment optional. Client incentive (CI; n=97) offered up to $100 in gift cards for intake and attendance during the first 30days of treatment. Contracting with staff incentives (CSI; n=49) consisted of meeting with an outpatient counselor prior to residential discharge, signing an attendance contract, receiving an appointment and payment to staff if clients attended. CSI significantly improved rates of successful transition (84%) and admission (74%) compared to UC (64% contact; 49% admitted). CI did not result in significantly improved outcomes (74%; 60%). CSI was likely mediated by the reliability (92 versus 52% in UC) and immediacy (1.0 versus 3.9days) of appointment scheduling. This study supports use of CSI for improving rates of transition between residential and outpatient continuing care treatment.

Determinants of Successful Treatment Outcomes Among a Sample of Urban American Indians/Alaska Natives: the Role of Social Environments. Spear S, Crevecoeur-Macphail D, Denering L, Dickerson D, Brecht M. J Behav Health Serv Res. 2013; 2013-2023.
Very few studies have analyzed the role of social environments on substance abuse treatment outcomes among urban American Indians/Alaska Natives (AI/ANs). This study examined a measure of positive treatment response-abstinence from substance use at treatment discharge-among urban AI/ANs in Los Angeles County. The sample included all AI/ANs in outpatient drug-free (e.g., no methadone) treatment and residential treatment from 2004 to 2008 (N = 811). Predictors of abstinence at discharge were (a) having recovery-oriented social support and (b) not having a difficult living situation (i.e., experiencing family conflict and/or living with someone who uses alcohol and/or drugs). Higher levels of recovery-oriented social support in the past 30 days predicted abstinence during outpatient treatment. In residential treatment, retention of 90 days or more, high recovery-oriented social support, and not experiencing difficult living situations predicted abstinence. Suggestions for optimizing treatment outcomes among AI/ANs and areas of further research are provided.

Public Support for Mandated Nicotine Reduction in Cigarettes. Pearson J, Abrams D, Niaura R, Richardson A, Vallone D. Am J Public Health. 2013; 103(3): 562-567.
The authors assessed public support for a potential Food and Drug Administration (FDA)-mandated reduction in cigarette nicotine content. They used nationally representative data from a June 2010 cross-sectional survey of US adults (n = 2649) to obtain weighted point estimates and correlates of support for mandated nicotine reduction. They also assessed the potential role of political ideology in support of FDA regulation of nicotine. Nearly 50% of the public supported mandated cigarette nicotine reduction, with another 28% having no strong opinion concerning this potential FDA regulation. Support for nicotine reduction was highest among Hispanics, African Americans, and those with less than a high school education.

Among smokers, the odds of supporting FDA nicotine regulation were 2.77 times higher among smokers who intended to quit in the next 6 months than among those with no plans to quit. The authors conclude that mandating nicotine reduction in cigarettes to non-addictive levels may reduce youth initiation and facilitate adult cessation. The reasons behind nicotine regulation need to be communicated to the public to preempt tobacco industry efforts to impede such a regulation.

Implementing Methadone Maintenance Treatment in Prisons in Malaysia. Wickersham J, Marcus R, Kamarulzaman A, Zahari M, Altice F. Bull World Health Organ. 2013; 91(2): 124-129.

In Malaysia, human immunodeficiency virus (HIV) infection is highly concentrated among people who inject opioids. For this reason, the country undertook a three-phase roll-out of a methadone maintenance treatment (MMT) program. In Phase 3, described in this paper, MMT was implemented within prisons and retention in care was assessed. After developing standard operating procedures and agreement between its Prisons Department and Ministry of Health, Malaysia established pilot MMT programs in two prisons in the states of Kelantan (2008) and Selangor (2009) - those with the highest proportions of HIV-infected prisoners. Community-based MMT programs were also established in Malaysia to integrate treatment activities after prisoners ' release. Having failed to reduce the incidence of HIV infection, in 2005 Malaysia embarked on a harm reduction strategy. Standard Operating Procedures were modified to: (i) escalate the dose of methadone more slowly; (ii) provide ongoing education and training for medical and correctional staff and inmates; (iii) increase the duration of methadone treatment before releasing prisoners; (iv) reinforce linkages with community MMT programs after prisoners' release; (v) screen for and treat tuberculosis; (vi) escalate the dose of methadone during treatment for HIV infection and tuberculosis; and (vii) optimize the daily oral dose of methadone (> 80 mg) before releasing prisoners. Prison-based MMT programs can be effectively implemented but require adequate dosing and measures are needed to improve communication between prison and police authorities, prevent police harassment of MMT clients after their release, and improve systems for tracking release dates.

Correlates of HIV Risk Behaviors among Homeless and Unstably Housed Young Adults. Logan J, Frye A, Pursell H, Anderson-Nathe M, Scholl J, Korthuis P. Public Health Rep. 2013; 128(3): 153-160.

Homeless young adults are exposed to multiple risk factors for HIV infection. The authors identified HIV risk behaviors and their correlates among homeless young adults in Portland, Oregon. They conducted a community-based, cross-sectional survey of HIV risk behaviors among homeless young adults aged 18-25 years in 2010. Participants completed three study components: (1) an interviewer-administered survey of HIV risk behaviors; (2) a brief, client-centered HIV risk-based counseling session; and (3) rapid HIV testing. Among 208 participants, 45.8% identified as racial/ethnic minority groups, 63.8% were male, and 35.7% self-identified as non-heterosexual. Six participants, all from sexual minority groups, had positive HIV screening results (two newly identified, four previously known) for a seropositivity rate of 2.9%. Female sex, belonging to a sexual minority group, frequent traveling between cities, depression, and alcohol use to intoxication were significantly associated with unprotected sex in univariate analysis. Female sex and high perceived risk of HIV were significantly associated with unprotected sex in multivariate analysis. These

findings support the need for enhanced HIV prevention interventions for homeless young adults.

Thirty-Day Hospital Readmission Rate among Adults Living with HIV. Berry SA, Fleishman JA, Yehia BR, Korthuis P, Todd Agwu AL, Moore RD, Gebo KA. for the HIV Research Network. AIDS Volume 27(10): 2013.
Thirty-day hospital readmission rate is receiving increasing attention as a quality of care indicator. The objective of this study was to determine readmission rates and to identify factors associated with readmission among persons living with HIV. The design was a prospective multicenter observational cohort in nine U.S. HIV clinics affiliated through the HIV Research Network. Patients engaged in HIV care during 2005-2010. Readmission rate was defined as the proportion of hospitalizations followed by a readmission within 30 days. Factors in multivariate analyses included diagnostic categories, patient demographic and clinical characteristics, and having an outpatient follow-up visit. Among 11,651 total index hospitalizations, the 30-day readmission rate was 19.3%. AIDS defining illnesses (ADI, 9.6% of index hospitalizations) and non-AIDS defining infections (26.4% of index hospitalizations) had readmission rates of 26.2% and 16.6%, respectively. Factors independently associated with readmission included lower CD4 count (AOR 1.80 [1.53, 2.11] for CD4.

Differences in HIV Risk Behavior Of Injection Drug Users in New York City by Health Care Setting. Turner A, Harripersaud K, Crawford N, Rivera A, Fuller C. AIDS Care. 2013: 1-9.
The purpose of this study is to examine the HIV risk behaviors and demographic characteristics of injection drug users (IDUs) by type of health care setting, which can inform development of tailored structural interventions to increase access to HIV prevention and medical treatment services. IDU syringe customers were recruited from pharmacies as part of the "Pharmacist As Resources Making Links to Community Services" (PHARM-Link) study, a randomized community-based intervention in New York City (NYC) aimed at connecting IDUs to HIV prevention, medical, and social services. An ACASI survey ascertained demographics, risk behavior, health-care utilization, and location where health care services were received in the past year. Data were analyzed using logistic regression. Of 602 participants, 34% reported receiving health care at a community clinic, 46% a private medical office, 15% a mobile medical unit, and 59% an emergency room (ER). After adjustment, participants who attended a community clinic were significantly more likely to have health insurance, report syringe sharing, and be HIV positive. Whites, nondaily injectors, insured, and higher income IDUs were more likely to attend a private medical office. Participants who recently used a case manager and had multiple sexual partners were more likely to use a mobile medical unit. ER attendees were more likely to be homeless and report recent drug treatment use. These findings show that IDU demographics and risk behaviors differ by health care setting, suggesting that risk reduction interventions should be tailored to health care settings. Specifically, these data suggest that community clinics and mobile medical units serve high-risk IDUs, highlighting the need for more research to develop and test innovative prevention and care programs within these settings.

Quitline Cessation Counseling for Young Adult Smokers: A Randomized Clinical Trial. Sims T, McAfee T, Fraser D, Baker T, Fiore M, Smith S. Nicotine Tob Res. 2013; 15(5): 932-941.

One in 5 young adults in the United States currently smoke, and young adults are less likely than other smokers to make aided quit attempts. Telephone quitlines may be a useful tool for treating this population. This study tested a quitline-based smoking cessation intervention versus mailed self-help materials in smokers 18-24 years old. This was a 2-group randomized clinical trial. The quitline-based counseling intervention (CI) included up to 4 proactive telephone counseling sessions; participants in the self-help (SH) group received only mailed cessation materials. Participants included 410 young adults who had smoked at least 1 cigarette in the past 30 days and who called the Wisconsin Tobacco Quit Line (WTQL) for help with quitting. Primary study outcomes included whether or not a quit date was set, whether or not a serious quit attempt was undertaken, and self-reported 7-day point-prevalence abstinence at 1-, 3-, and 6-month post-enrollment. The CI and SH groups did not differ in the intent-to-treat abstinence analyses at any of the follow-ups. However, the CI group was significantly more likely to set a quit date at 1-month post-enrollment. Follow-up response rates were low (67.8% at 1 month; 53.4% at 3 months; and 48.3% at 6 months) reflecting lower motivation to participate in this kind of research. The authors conclude that relative to self-help, quitline counseling motivated young adults to set a quit date but abstinence rates were not improved. Research is needed on how to motivate young adult smokers to seek cessation treatment including quitline services.

Clinicians' Perceptions of Implementation Effectiveness of 100% Tobacco-Free Practices: A Longitudinal Study of New York State. Eby L, Laschober T. J Behav Health Serv Res. 2013; Epub ahead of print.

In 2008, the state of New York required substance use disorder treatment organizations to be 100% tobacco-free. This longitudinal study examined clinicians' perceptions of the implementation extensiveness of the tobacco-free practices approximately 10-12 months (Time 1) and 20-24 months (Time 2) post regulation and investigated whether clinicians' commitment to change and use of provided resources at Time 1 predicts perceptions of implementation extensiveness at Time 2. Clinicians (N=287) noted a mean implementation of 5.60 patient practices (0-10 scale), 2.33 visitor practices (0-8 scale), and 6.66 employee practices (0-12 scale) at Time 1. At Time 2, clinicians perceived a mean implementation of 5.95 patient practices (no increase from Time 1), 2.89 visitor practices (increase from Time 1), and 7.12 employee practices (no increase from Time 1). Commitment to change and use of resources positively predicted perceived implementation extensiveness of visitor and employee practices. The use of resources positively predicted implementation for patient practices.

Retention in Methadone and Buprenorphine Treatment among African Americans. Gryczynksi J, et al. Journal of Substance Abuse Treatment, 2013.

Methadone has been the most commonly used pharmacotherapy for the treatment of opioid dependence in U.S. public sector treatment, but availability of buprenorphine as an alternative medication continues to increase. Drawing data from two community-based clinical trials that were conducted nearly contemporaneously, this study examined retention in methadone versus buprenorphine treatment over 6 months among urban African Americans receiving treatment in one of four publicly-funded programs (*N* = 478; 178 methadone; 300 buprenorphine).

Adjusting for confounds related to medication selection, survival analysis revealed that buprenorphine patients are at substantially higher risk of dropout compared to methadone patients (HR = 2.43; $p < .001$). Buprenorphine's retention disadvantage appears to be concentrated in the earlier phases of treatment (approximately the first 50 days), after which risk of subsequent dropout becomes similar for the two medications. These findings confirm a retention disparity between methadone and buprenorphine in this population, and suggest potential avenues for future research to enhance retention in buprenorphine treatment.

Correspondence of Motivational Interviewing Adherence and Competence Ratings in Real and Role-Played Client Sessions. Decker S, Carroll K, Nich C, Canning-Ball M, Martino S. Psychol Assess. 2013; 25(1): 306-312.
Treatment integrity ratings (adherence and competence) are frequently used as outcome measures in clinician training studies, drawn from recorded real client or role-played client sessions. However, it is unknown whether clinician adherence and competence are similar in real client and role-played sessions or whether real and role-play clients provide similar opportunities for skill demonstration. In this study, the authors examined the correspondence of treatment adherence and competence ratings obtained in real client and role-played sessions for 91 clinicians trained in motivational interviewing (MI), using data from a multisite trial examining 3 methods of clinician training (Martino et al., 2011). Results indicated overall poor integrity rating correspondence across the 2 session types, as indicated by weak correlations (rs=.05-.27). Clinicians were rated significantly more MI adherent overall and specifically used more advanced MI strategies in role-played than real client sessions at several assessment time points (ds=0.36, 0.42). Real clients, in comparison to the role-play actor, demonstrated greater motivation at the beginning of the session (d=1.09), discussion of unrelated topics (d=0.70), and alliance with the clinician (d=0.72). These findings suggest that MI integrity rating data obtained from real client and role-played sessions may not be interchangeable. More research is needed to improve the procedures and psychometric strength of treatment integrity assessment based on role-played sessions.

Development of the Therapist Empathy Scale. Decker S, Nich C, Carroll K, Martino S. Behav Cogn Psychother. 2013; Epub ahead of print.
Few measures exist to examine therapist empathy as it occurs in session. A 9-item observer rating scale, called the Therapist Empathy Scale (TES), was developed based on Watson's (1999) work to assess affective, cognitive, attitudinal, and attunement aspects of therapist empathy. The aim of this study was to evaluate the inter-rater reliability, internal consistency, and construct and criterion validity of the TES. Raters evaluated therapist empathy in 315 client sessions conducted by 91 therapists, using data from a multi-site therapist training trial (Martino et al., 2010) in Motivational Interviewing (MI). Inter-rater reliability (ICC = .87 to .91) and internal consistency (Cronbach's alpha = .94) were high. Confirmatory factor analyses indicated some support for single-factor fit. Convergent validity was supported by correlations between TES scores and MI fundamental adherence (r range .50 to .67) and competence scores (r range .56 to .69). Discriminant validity was indicated by negative or non-significant correlations between TES and MI-inconsistent behavior (r range .05 to -.33). The TES demonstrates excellent inter-rater reliability and internal consistency. Results indicate some support for a single-factor solution and convergent and discriminant validity. Future studies

should examine the use of the TES to evaluate therapist empathy in different psychotherapy approaches and to determine the impact of therapist empathy on client outcome.

Using Electronic Health Records to Assess Substance Abuse and Psychiatric Comorbidities. Wu L, Gersing K, Swartz M, Burchett B, Li T, Blazer D. J Psychiatr Res. 2013; 47(4): 555-563.

The objective of this study was to examine prevalences of substance use disorders (SUD) and comprehensive patterns of comorbidities among psychiatric patients ages 18-64 years (N = 40,099) in an electronic health records (EHR) database. DSM-IV diagnoses among psychiatric patients in a large university system were systematically captured: SUD, anxiety (AD), mood (MD), personality (PD), adjustment, childhood-onset, cognitive/dementia, dissociative, eating, factitious, impulse-control, psychotic (schizophrenic), sexual/gender identity, sleep, and somatoform diagnoses. Comorbidities and treatment types among patients with a SUD were examined. Among all patients, 24.9% (n = 9984) had a SUD, with blacks (35.2%) and Hispanics (32.9%) showing the highest prevalence. Among patients with a SUD, MD was prevalent across all age groups (50.2-56.6%). Patients aged 18-24 years had elevated odds of comorbid PD, adjustment, childhood-onset, impulse-control, psychotic, and eating diagnoses. Females had more PD, AD, MD, eating, and somatoform diagnoses, while males had more childhood-onset, impulse-control, and psychotic diagnoses. Blacks had greater odds than whites of psychotic and cognitive/dementia diagnoses, while whites exhibited elevated odds of PA, AD, MD, childhood-onset, eating, somatoform, and sleep diagnoses. Women, blacks, and Native American/multiple-race adults had elevated odds of using inpatient treatment; men, blacks, and Hispanics had increased odds of using psychiatric emergency care. Comorbid MD, PD, adjustment, somatoform, psychotic, or cognitive/dementia diagnoses increased inpatient treatment. Patients with a SUD, especially minority members, use more inpatient or psychiatric emergency care than those without. Findings provide evidence for research on understudied diagnoses and underserved populations in the real-world clinical settings.

Medicaid Care Management: Description of High-Cost Addiction Treatment Clients. Neighbors C, Sun Y, Yerneni R, Tesiny E, Burke C, Bardsley L, McDonald R, Morgenstern J. J Subst Abuse Treat. 2013; Epub ahead of print.

High utilizers of alcohol and other drug treatment (AODTx) services are a priority for healthcare cost control. The authors examine characteristics of Medicaid-funded AODTx clients, comparing three groups: individuals < 90th percentile of AODTx expenditures (n = 41,054); high-cost clients in the top decile of AODTx expenditures (HC; n = 5,718); and 1760 enrollees in a chronic care management (CM) program for HC clients implemented in 22 counties in New York State. Medicaid and state AODTx registry databases were combined to draw demographic, clinical, social needs and treatment history data. HC clients accounted for 49% of AODTx costs funded by Medicaid. As expected, HC clients had significant social welfare needs, comorbid medical and psychiatric conditions, and use of inpatient services. The CM program was successful in enrolling some high-needs, high-cost clients but faced barriers to reaching the most costly and disengaged individuals.

Developmental Trajectories of Childhood Obesity and Risk Behaviors in Adolescence. Huang DY, Lanza HI, Wright-Volel K, Anglin MD. J Adolesc. 2013; 36: 139-148.
Using group-based trajectory modeling, this study examined 5,156 adolescents from the child sample of the 1979 National Longitudinal Survey of Youth to identify developmental trajectories of obesity from ages 6–18 and evaluate associations of such trajectories with risk behaviors and psychosocial health in adolescence. Four distinctive obesity trajectories were identified: "Chronically Obese," "Decreasing," "Increasing," and "Non-obese." Males were overrepresented in the Chronically Obese and Increasing groups; females were overrepresented in the Decreasing group. African-Americans were overrepresented in the Chronically Obese, Increasing, and Decreasing groups; in contrast, Whites were overrepresented in the Non-obese group. Obesity trajectories were not associated with greater trends in alcohol use, marijuana use, or delinquency, but Chronically Obese adolescents showed a greater increase in cigarette smoking over time compared to other trajectories. The Increasing trajectory, representing a transition into obesity status from childhood to adolescence, was associated with poorer psychosocial health compared to other trajectories.

Taxometric Analysis of DSM-IV and DSM-5 Alcohol use Disorders. Kerridge BT, Saha TD, Gmel G, Rehm J. Drug Alcohol Depend. 2013; 129: 60-69.
With preparations currently being made for the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5), one prominent issue to resolve is whether alcohol use disorders are better represented as discrete categorical entities or as a dimensional construct. The purpose of this study was to investigate the latent structure of DSM-4th edition (DSM-IV) and proposed DSM-5 alcohol use disorders. The study used the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to conduct taxometric analyses of DSM-IV and DSM-5 alcohol use disorders defined by different thresholds to determine the taxonic or dimensional structure underlying the disorders. DSM-IV and DSM-5 alcohol abuse and dependence criteria with 3+ thresholds demonstrated a dimensional structure. Corresponding thresholds with 4+ criteria were clearly taxonic, as were thresholds defined by cut-offs of 5+ and 6+ criteria. The authors conclude that DSM-IV and DSM-5 alcohol use disorders demonstrated a hybrid taxonic-dimensional structure. That is, DSM-IV and DSM-5 alcohol use disorders may be taxonically distinct compared to no disorder if defined by a threshold of 4 or more criteria. However, there may be dimensional variation remaining among non-problematic to subclinical cases. A careful and systematic program of structural research using taxometric and psychometric procedures is warranted.

Reports of Drinking to Self-Medicate Anxiety Systems: Longitudinal Assessment for Subgroups of Individuals with Alcohol Dependence. Crum RM, La Flair L, Storr CL, Green KM, Stuart EA, Alvanzo AA, Lazareck S, Bolton JM, Robinson J, Sareen J, Mojtabai R. Depress Anxiety. 2013; 30: 174-183.
Self-medication with alcohol is frequently hypothesized to explain anxiety and alcohol dependence comorbidity. Yet, there is relatively little assessment of drinking to self-medicate anxiety and its association with the occurrence or persistence of alcohol dependence in population-based longitudinal samples, or associations within demographic and clinical subgroups. Hypothesizing that self-medication of anxiety with alcohol is associated with the subsequent occurrence and persistence of alcohol dependence, the authors assessed these associations using data from the National Epidemiologic Survey on Alcohol and Related

Conditions, and examined these associations within population subgroups. This nationally representative survey of the US population included 43,093 adults surveyed in 2001-2002 and 34,653 re-interviewed in 2004-2005. Logistic regression incorporating propensity score methods was used. Reports of drinking to self-medicate anxiety was associated with the subsequent occurrence (adjusted odds ratio (AOR) = 5.71, 95% confidence interval (CI) = 3.56-9.18, P < .001) and persistence (AOR = 6.25, CI = 3.24-12.05, P < .001) of alcohol dependence. The estimated proportions of the dependence cases attributable to self-medication drinking were 12.7 and 33.4% for incident and persistent dependence, respectively. Stratified analyses by age, sex, race-ethnicity, anxiety disorders and sub-threshold anxiety symptoms, quantity of alcohol consumption, history of treatment, and family history of alcoholism showed few subgroup differences. The authors conclude that individuals who report drinking to self-medicate anxiety are more likely to develop alcohol dependence, and the dependence is more likely to persist. There is little evidence for interaction by the population subgroups assessed. Self-medication drinking may be a useful target for prevention and intervention efforts aimed at reducing the occurrence of alcohol dependence.

Build a Better Mouse: Directly-Observed Issues in Computer Use for Adults with SMI. Black A, Serowik K, Schensul J, Bowen A, Rosen M. Psychiatr Q. 2013; 84(1): 81-92.
Integrating information technology into healthcare has the potential to bring treatment to hard-to-reach people. Individuals with serious mental illness (SMI), however, may derive limited benefit from these advances in care because of lack of computer ownership and experience. To date, conclusions about the computer skills and attitudes of adults with SMI have been based primarily on self-report. In the current study, 28 psychiatric outpatients with co-occurring cocaine use were interviewed about their computer use and opinions, and 25 were then directly observed using task analysis and think aloud methods as they navigated a multi-component health informational website. Participants reported low rates of computer ownership and use, and negative attitudes towards computers. Self-reported computer skills were higher than demonstrated in the task analysis. However, some participants spontaneously expressed more positive attitudes and greater computer self-efficacy after navigating the website. Implications for increasing access to computer-based health information are discussed.

Do Race, Ethnicity, and Psychiatric Diagnoses Matter in the Prevalence Of Multiple Chronic Medical Conditions? Cabassa L, Humensky J, Druss B, Lewis-Fernández R, Gomes A, Wang S, Blanco C. Med Care. 2013; 51(6): 540-547.
The proportion of people in the United States with multiple chronic medical conditions (MCMC) is increasing. Yet, little is known about the relationship that race, ethnicity, and psychiatric disorders have on the prevalence of MCMCs in the general population. This study used data from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (N=33,107). Multinomial logistic regression models adjusting for socio-demographic variables, body mass index, and quality of life were used to examine differences in the 12-month prevalence of MCMC by race/ethnicity, psychiatric diagnosis, and the interactions between race/ethnicity and psychiatric diagnosis. Compared to non-Hispanic Whites, Hispanics reported lower odds of MCMC and African Americans reported higher odds of MCMC after adjusting for covariates. People with psychiatric disorders reported higher odds of MCMC compared with people without psychiatric disorders. There were significant interactions between race and psychiatric diagnosis associated with rates of MCMC. In the

presence of certain psychiatric disorders, the odds of MCMC were higher among African Americans with psychiatric disorders compared to non-Hispanic Whites with similar psychiatric disorders. This study's results indicate that race, ethnicity, and psychiatric disorders are associated with the prevalence of MCMC. As the rates of MCMC rise, it is critical to identify which populations are at increased risk and how to best direct services to address their health care needs.

A Tutorial on Propensity Score Estimation for Multiple Treatments Using Generalized Boosted Models. McCaffrey D, Griffin B, Almirall D, Slaughter M, Ramchand R, Burgette L. Stat Med. 2013: 1-27.

The use of propensity scores to control for pretreatment imbalances on observed variables in non-randomized or observational studies examining the causal effects of treatments or interventions has become widespread over the past decade. For settings with two conditions of interest such as a treatment and a control, inverse probability of treatment weighted estimation with propensity scores estimated via boosted models has been shown in simulation studies to yield causal effect estimates with desirable properties. There are tools (e.g., the twang package in R) and guidance for implementing this method with two treatments. However, there is not such guidance for analyses of three or more treatments. The goals of this paper are twofold: (1) to provide step-by-step guidance for researchers who want to implement propensity score weighting for multiple treatments and (2) to propose the use of generalized boosted models (GBM) for estimation of the necessary propensity score weights. The authors define the causal quantities that may be of interest to studies of multiple treatments and derive weighted estimators of those quantities. They present a detailed plan for using GBM to estimate propensity scores and using those scores to estimate weights and causal effects. They also provide tools for assessing balance and overlap of pretreatment variables among treatment groups in the context of multiple treatments. A case study examining the effects of three treatment programs for adolescent substance abuse demonstrates the methods.

Pilot of a Brief, Web-Based Educational Intervention Targeting Safe Storage and Disposal of Prescription Opioids. McCauley JL, Back SE, Brady KT. Addict Behav. 2013 Jun; 38(6): 2230-2235. doi: 10.1016/j.addbeh.2013.01.019. E-pub 2013 Feb 4.

Prescription opioid misuse has been declared an American epidemic and a significant proportion of misused opioids are diverted from legitimate prescriptions. Patient education regarding appropriate use and the dangers of misuse has been identified as a key intervention target. The current study presents findings from the open pilot of a patient-tailored, brief, web-based intervention designed to improve knowledge of safe medication use, storage and disposal. Subjects were 62 treatment-seeking outpatients at two diverse outpatient health clinics (dental and pain management) who were prescribed an opioid medication. Subjects completed an online assessment of risk factors for prescription opioid misuse and the 15-minute Script Safety intervention. Knowledge and misuse behaviors were assessed at baseline, immediately post intervention (knowledge only) and at one-week and one-month follow up. Knowledge regarding safe prescription opioid use, storage and disposal improved significantly from pre to post intervention and was sustained at follow up (% correct from baseline to one-month follow up: unsafe to retain unused pills, 66.1% vs. 96.5%; unsafe to borrow pills from family/friends, 87.1% vs. 98.2%; best to store pills in cool, dry, secure location, 45.2% vs. 89.5%; not recommended to use expired medications, 75.8% vs. 96.5%; not recommended to

flush all medications down the toilet, 45.2% vs. 82.5%, ps <.01). Reductions in self-reported misuse behaviors were also observed. Although preliminary, the findings highlight the potential utility of integrating brief, web-based educational interventions in community and primary health care settings.

The Moderating Effects of Skin Color and Ethnic Identity Affirmation on Suicide Risk among Low-SES African American Women. Perry B, Stevens-Watkins D, Oser C. Race Soc Probl. 2013; 5(1): 1-14.
This study examined the influence of concurrent racism and sexism experiences (i.e. gendered racism) on African American women's suicidal ideation and behavior in the context of disadvantaged socioeconomic status. Drawing on a stress process framework, the moderating effects of ethnic identity and skin color were explored using multiple regression analyses. Data were from 204 low-income African American women in the B-WISE (Black Women in a Study of Epidemics) project. Findings suggested that experiencing gendered racism significantly increased these women's risk for suicidal ideation or behavior, though only among women with medium or dark skin color. Also, having strong ethnic identity buffered the harmful effects of gendered racism. The moderating properties of skin color and ethnic identity affirmation likely operate through psychosocial pathways, blocking internalization of negative stereotypes and reducing the level of distress experienced in response to gendered racism.

Correlates of Reasons for Not Reporting Rape to Police: Results from A National Telephone Household Probability Sample of Women with Forcible Or Drug-or-Alcohol Facilitated/Incapacitated Rape. Cohn AM, Zinzow HM, Resnick HS, Kilpatrick DG. J Interpers Violence. 2013; 28(3): 455-473.
Rape tactics, rape incident characteristics, and mental health problems (lifetime depression, PTSD, and substance abuse) were investigated as correlates of eight different reasons for not reporting a rape to police among women who had experienced but did not report a rape to police (n = 441) within a national telephone household probability sample. Rape tactics (non-mutually exclusive) included drug or alcohol-facilitated or incapacitated rape (DAFR/IR; n = 119) and forcible rape (FR; n = 376). Principal Components Analysis (PCA) was conducted to extract a dominant set of patterns among the eight reasons for not reporting, and to reduce the set of dependent variables. PCA results indicated three unique factors: Not Wanting Others to Know, Non-acknowledgment of Rape, and Criminal Justice Concerns. Hierarchical regression analyses showed DAFR/IR and FR were both positively and significantly associated with Criminal Justice Concerns, whereas DAFR/IR, but not FR, was associated with Non-acknowledgment as a reason for not reporting to police. Neither DAFR/IR nor FR emerged as significant predictors of Others Knowing after controlling for fear of death or injury at the time of the incident. Correlations among variables showed that the Criminal Justice Concerns factor was positively related to lifetime depression and PTSD and the Non-acknowledgement factor was negatively related to lifetime PTSD. Findings suggest prevention programs should educate women about the definition of rape, which may include incapacitation due to alcohol or drugs, to increase acknowledgement and decrease barriers to police reporting.

Drug-Abusing Offenders with Co-Morbid Mental Disorders: Gender Differences in Problem Severity, Treatment Participation, and Recidivism. Du J, Huang D, Zhao M, Hser Y-I. Biomed Environ Sci. 2013; 26(1): 32-39.
This study examined the gender differences in drug-related problems and predictors of recidivism among a sample of 1,444 offenders with co-morbid drug abuse and mental disorders participating in California's Proposition 36 Program. Background characteristics and problem severity in multiple key life areas were assessed at intake by using Addiction Severity Index, and drug treatment participation, mental health diagnoses and arrests were based on official records. Women demonstrated greater problem severity than men in family relationships, health, psychological health, and sexual and physical abuse history. Men on the other hand had greater criminal history, high rates of attention disorder, and psychotic disorder. More men than women were rearrested during the year after treatment admission. Logistic regression analyses showed that for the combined sample, male, young age, cocaine use (relative to methamphetamine), drug abuse severity, methadone treatment, arrest history and fewer prior treatment history were associated with higher recidivism at 12-month follow-up; lower education, cocaine use, and arrest history were related to women's recidivism, while young age, outpatient treatment, and arrest history were predictors of men's recidivism. Although the specific type of mental disorder did not seem to be predictive of recidivism, the high rates of mental health disorder and arrest of this population is problematic. Intervention strategies taking into consideration gender-specific problems and needs can improve outcomes for both.

Factors Affecting the Sustainability of Self-Run Recovery Homes in the United States. Harvey R, Mortensen J, Aase D, Ferrari JR, Jason L. Int J Self Help Self Care. 2013; 7(1): 99-109.
This study examined the sustainability rates of 214 self-run substance abuse recovery homes called Oxford Houses (OHs) over a six-year period. The authors list five factors needed to sustain an OH: affordable housing, residents following OH principles, resident income, institutional support, and community support. Results indicated a high sustainability rate (86.9%) in which 186 OHs remained open and 28 OHs closed. Reasons for houses closing (N = 14) included lack of affordable housing, which we classified as an external factor. Houses that closed because of internal factors (N = 13) included residents who were unable to adhere to OH rules, and insufficient income of residents. No house-level differences for income, sense of community, average lengths of stay, house age, or neighborhood characteristics were found between the houses that closed versus houses that remained open. Because the OH system relies on residents to sustain individual houses located in ordinary residential neighborhoods, these findings suggest that OH sustainability depends on locale, primarily access to affordable housing and adequate job opportunities for residents.

Measurement of Predictive Validity in Violence Risk Assessment Studies: A Second-Order Systematic Review. Singh JP, Desmarais SL, Van Dorn RA. Behav Sci Law. 2013; 31(1): 55-73.
The objective of the present review was to examine how predictive validity is analyzed and reported in studies of instruments used to assess violence risk. The authors reviewed 47 predictive validity studies published between 1990 and 2011 of 25 instruments that were included in two recent systematic reviews. Although all studies reported receiver operating

characteristic curve analyses and the area under the curve (AUC) performance indicator, this methodology was defined inconsistently and findings often were misinterpreted. In addition, there was between-study variation in benchmarks used to determine whether AUCs were small, moderate, or large in magnitude. Though virtually all of the included instruments were designed to produce categorical estimates of risk - through the use of either actuarial risk bins or structured professional judgments - only a minority of studies calculated performance indicators for these categorical estimates. In addition to AUCs, other performance indicators, such as correlation coefficients, were reported in 60% of studies, but were infrequently defined or interpreted. An investigation of sources of heterogeneity did not reveal significant variation in reporting practices as a function of risk assessment approach (actuarial vs. structured professional judgment), study authorship, geographic location, type of journal (general vs. specialized audience), sample size, or year of publication. Findings suggest a need for standardization of predictive validity reporting to improve comparison across studies and instruments.

Psychosocial Functioning among Inmates in Prison-Based Drug Treatment: Results from Project BRITE. Burdon WM, St De Lore J, Dang J, Warda US, Prendergast ML. J Exp Criminol. 2013; 9(1): 45-64.

The objective of this study was to assess the impact of a positive behavioral reinforcement intervention on psychosocial functioning of inmates over the course of treatment and on post-treatment self-reported measures of treatment participation, progress, and satisfaction. Male (n = 187) and female (n = 143) inmates participating in 12-week prison-based Intensive Outpatient (IOP) drug treatment were randomly assigned to receive standard treatment (ST) or standard treatment plus positive behavioral reinforcement (BR) for engaging in targeted activities and behaviors. Participants were assessed for psychosocial functioning at baseline and at the conclusion of treatment (post-treatment). Self-reported measures of treatment participation, treatment progress, and treatment satisfaction were also captured at post-treatment. The intervention affected female and male subjects differently and not always in a way that favored BR subjects, as compared to the ST subjects, most notably on measures of depression and criminal thinking. Possible explanations for the results include differences in the male and female custody environments combined with the procedures that study participants had to follow to earn and/or receive positive reinforcement at the two study sites, as well as baseline differences between the genders and a possible floor effect among females on measures of criminality. Limitations of the study included the inability to make study participants blind to the study conditions and the possible over-branding of the study, which may have influenced the results.

CTN-RELATED RESEARCH

An Intronic Variant in OPRD1 Predicts Treatment Outcome for Opioid Dependence in African-Americans. Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Neuropsychopharmacology. 2013 Apr 23. [Epub ahead of print].

Although buprenorphine and methadone are both effective treatments for opioid dependence, their efficacy can vary significantly among patients. Genetic differences may explain some of the variability in treatment outcome. Understanding the interactions between genetic background and pharmacotherapy may result in more informed treatment decisions. This study is a pharmacogenetic analysis of the effects of genetic variants in OPRD1, the gene encoding the δ-opioid receptor, on the prevalence of opioid-positive urine tests in African-Americans (n=77) or European-Americans (n=566) undergoing treatment for opioid dependence. Patients were randomly assigned to treatment with either methadone or buprenorphine/naloxone (Suboxone) over a 24-week open-label clinical trial, in which illicit opioid use was measured by weekly urinalysis. In African-Americans, the intronic SNP rs678849 predicted treatment outcome for both medications. Methadone patients with the CC genotype were less likely to have opioid-positive urine tests than those in the combined CT and TT genotypes group (relative risk (RR)=0.52, 95% confidence interval (CI)=0.44-0.60, p=0.001). In the buprenorphine treatment group, however, individuals with the CC genotype were more likely to have positive opioid drug screens than individuals in the combined CT and TT genotypes group (RR=2.17, 95% CI=1.95-2.68, p=0.008). These findings indicate that the genotype at rs678849 predicts African-American patient response to two common treatments for opioid dependence, suggesting that matching patients to treatment type based on the genotype at this locus may improve overall treatment efficacy. This observation requires confirmation in an independent population.

Association of Cannabis Use With Opioid Outcomes Among Opioid-Dependent Youth. Hill KP, Bennett HE, Griffin ML, Connery HS, Fitzmaurice GM, Subramaniam G, Woody GE, Weiss RD. Drug Alcohol Depend. 2013 Mar 22. [Epub ahead of print].

Cannabis use is common among opioid-dependent patients, but studies of its association with treatment outcome are mixed. In this secondary analysis, the association of cannabis use with opioid treatment outcome is assessed. In the main study, participants (n=152) aged 15-21 years were randomized to receive psychosocial treatments and either a 12-week course of buprenorphine-naloxone with a dose taper to zero in weeks 9-12, or a 2-week detoxification with buprenorphine-naloxone. Drug use was assessed by self-report and urine drug screen at baseline and during study weeks 1-12. The association between cannabis and opioid use at weeks 4, 8, and 12 was examined using logistic regression models. Participants reported a median of 3.0 days (range=0-30) cannabis use in the past month; half (50.3%; n=77) reported occasional use, one-third reported no use (33.1%; n=50), and one-sixth reported daily cannabis use (16.6%; n=25). Median lifetime cannabis use was 4.0 years (range=0-11) and median age of initiation of use was 15.0 years (range 9-21). Neither past cannabis use (age of initiation and use in the month prior to baseline) nor concurrent use was associated with level of opioid use. Overall, cannabis use had no association with opioid use over 12 weeks in this sample of opioid-dependent youth. While cannabis use remains potentially harmful, it was not a predictor of poor opioid treatment outcome.

Buprenorphine/Naloxone and Methadone Maintenance Treatment Outcomes for Opioid Analgesic, Heroin, and Combined Users: Findings From Starting Treatment With Agonist Replacement Therapies (START). Potter JS, Marino EN, Hillhouse MP, Nielsen S, Wiest K, Canamar CP, Martin JA, Ang A, Baker R, Saxon AJ, Ling W. J Stud Alcohol Drugs. 2013 Jul; 74(4): 605-613.

The objective of this secondary analysis was to explore differences in baseline clinical characteristics and opioid replacement therapy treatment outcomes by type (heroin, opioid analgesic [OA], or combined [heroin and OA]) and route (injector or non-injector) of opioid use. A total of 1,269 participants (32.2% female) were randomized to receive one of two study medications (methadone or buprenorphine/naloxone [BUP]). Of these, 731 participants completed the 24-week active medication phase. Treatment outcomes were opioid use during the final 30 days of treatment (among treatment completers) and treatment attrition. Non-opioid substance dependence diagnoses and injecting differentiated heroin and combined users from OA users. Non-opioid substance dependence diagnoses and greater heroin use differentiated injectors from non-injectors. Further, injectors were more likely to be using at end of treatment compared with non-injectors. OA users were more likely to complete treatment compared with heroin users and combined users. Non-injectors were more likely than injectors to complete treatment. There were no interactions between type of opioid used or injection status and treatment assignment (methadone or BUP) on either opioid use or treatment attrition. Findings indicate that substance use severity differentiates heroin users from OA users and injectors from non-injectors. Irrespective of medication, heroin use and injecting are associated with treatment attrition and opioid misuse during treatment. These results have particular clinical interest, as there is no evidence of superiority of BUP over methadone for treating OA users versus heroin users.

Preliminary Evaluation Of A Model Of Stimulant Use, Oxidative Damage and Executive Dysfunction. Winhusen T, Walker J, Brigham G, Lewis D, Somoza E, Theobald J, Somoza V. Am J Drug Alcohol Abuse. 2013 Jul; 39(4): 227-234. Epub 2013 Jun 28.

Illicit stimulant use increases oxidative stress and oxidative stress has been found to be associated with deficits in memory, attention and problem-solving. The objective of this study was to test a model of the association among oxidative DNA damage, a severe form of oxidative stress, and stimulant use, executive function and stimulant-use outcomes. Six sites evaluating 12-step facilitation for stimulant abusers obtained peripheral blood samples from methamphetamine-dependent (n=45) and cocaine-dependent (n=120) participants were examined. The blood samples were submitted to a comet assay to assess oxidative DNA damage. Executive Dysfunction was assessed with the Frontal Systems Behavior Scale (FrSBe), which is a reliable and valid self-report assessment of executive dysfunction, disinhibition and apathy. Stimulant-use measures included self-reported stimulant use and stimulant urine drug screens (UDS). While more recent cocaine use (<30 days abstinence) was associated with greater oxidative DNA damage ($W=2.4$, $p<0.05$, $d=0.36$), the results did not support the hypothesized relationship between oxidative DNA damage, executive dysfunction and stimulant use outcomes for cocaine-dependent patients. Support for the model was found for methamphetamine-dependent patients, with oxidative DNA damage significantly greater in methamphetamine-dependent patients with executive dysfunction ($W=2.2$, $p<0.05$, $d=0.64$) and with executive dysfunction being a significant mediator of oxidative DNA damage and stimulant use during active treatment ($ab=0.089$, $p<0.05$). As predicted, neither disinhibition

nor apathy were significant mediators of oxidative damage and future stimulant use. These findings provide preliminary support for a model in which oxidative damage resulting from methamphetamine use results in executive dysfunction, which in turn increases vulnerability to future stimulant use.

Reductions In Anxiety and Depression Symptoms In Youth Receiving Substance Use Treatment. Horigian VE, Weems CF, Robbins MS, Feaster DJ, Ucha J, Miller M, Werstlein R.
Am J Addict. 2013 Jul; 22(4): 329-337.
Research shows that interventions for substance use disorders may be helpful in reducing internalizing disorders in adolescents. This paper examines the prevalence and reductions of anxiety and depression symptoms among youth receiving substance use treatment. Four hundred eighty adolescents ages 12-17 who received treatment for substance abuse as part of the Brief Strategic Family Therapy effectiveness trial were screened for anxiety and depression using the Diagnostic Interview Schedule for Children-Predictive Scales (DISC-PS). Twelve-month post-randomization assessments were completed by 327 parents and 315 youth. Sixty-five percent of the sample was found to have probability of at least one anxiety disorder or depression diagnosis. Significant reduction of anxiety and depressive symptoms and significant reductions in probable anxiety and depression diagnoses were observed at follow-up. Few differences by treatment type and by ethnic group were noticed. Findings indicate that substance use interventions might help reduce the prevalence of anxiety and depressive symptoms and the probability of these disorders.

Synergy between Seeking Safety and Twelve-Step Affiliation on Substance Use Outcomes For Women. Morgan-Lopez AA, Saavedra LM, Hien DA, Campbell AN, Wu E, Ruglass L. J Subst Abuse Treat. 2013 Apr 1. [Epub ahead of print].
The Recovery Management paradigm provides a conceptual framework for the examination of joint impact of a focal treatment and post-treatment service utilization on substance abuse treatment outcomes. The authors test this framework by examining the interactive effects of a treatment for comorbid PTSD and substance use, Seeking Safety, and post-treatment Twelve-Step Affiliation (TSA) on alcohol and cocaine use. Data from 353 women in a six-site, randomized controlled effectiveness trial within the NIDA Clinical Trials Network were analyzed under latent class pattern mixture modeling. LCPMM was used to model variation in Seeking Safety by TSA interaction effects on alcohol and cocaine use. Significant reductions in alcohol use among women in Seeking Safety (compared to health education) were observed; women in the Seeking Safety condition who followed up with TSA had the greatest reductions over time in alcohol use. Reductions in cocaine use over time were also observed but did not differ between treatment conditions nor were there interactions with post-treatment TSA. Findings advance understanding of the complexities for treatment and continuing recovery processes for women with PTSD and SUDs, and further support the chronic disease model of addiction.

Opioid Use Disorders in Adolescents: A Review of Prevalence, Problems, Clinical Features and Treatment Options. Subramaniam GA. Adolescent Psychiatry 2013 April; 3(2): 117-122.

Rates of opioid misuse among adolescents have risen to epidemic proportions. A prescription opioid analgesic is the second most commonly chosen substance among those initiating substance misuse, next only to marijuana. Soaring rates of treatment admissions among youth with opioid problems and reports of overdose deaths from prescription opioid analgesics and heroin make this issue of substantial public health concern. The objective of this article is to provide both clinicians and administrators a succinct and comprehensive review of the topic to assist them in incorporating evidence-based treatments, including medications to address the complex needs of this highly comorbid but treatable population of youth. This article synthesized the published literature on the epidemiology of heroin use and misuse of prescription opioids among youth in community samples; summarized findings on demographic and social characteristics and cooccurring problems in multiple arenas such as academic, substance use, psychiatric, criminal activity and risk for hepatitis- C and HIV infections; briefly reviewed access, diversion patterns and progression of opioid use; provided an overview of the existing medication-assisted treatment efficacy literature; and factors that impact treatment outcomes. The author concluded that physicians, especially adolescent psychiatrists, are well positioned to effectively treat this highly comorbid population and potentially arrest its persistence into adulthood, which in turn bears high direct and indirect societal costs.

Psychometric Properties of a Spanish-Language Version of the Short Inventory of Problems. Kiluk BD, Dreifuss JA, Weiss RD, Horigian VE, Carroll KM. Psychol Addict Behav. 2013 Jun 17. [Epub ahead of print].

Hispanic Americans are substantially underrepresented in clinical and research samples for substance use treatment, with language cited as one of the major barriers to their participation, indicating a need for more validated assessments in Spanish. This study evaluated the psychometric properties of a Spanish version of the Short Inventory of Problems (SIP), used in a multisite, randomized trial conducted for Spanish-speaking substance users. The sample included 405 Spanish-speaking treatment seekers, mostly male (88%) and legally mandated to treatment (71%). The Spanish version of the revised SIP (SIP-RS), as well as other commonly used assessment measures translated into Spanish, were administered at baseline and at the end of treatment. Internal consistency was excellent ($\alpha = .96$), and construct validity was supported through correlations with composite scores from the Addiction Severity Index (ASI) (e.g., $r = .57$, $p < .01$ for ASI drug composite), and through differential SIP-RS scores according to diagnostic criteria. The SIP-RS also demonstrated an association with substance use and treatment retention, with higher baseline scores associated with significantly less abstinence during treatment ($\beta = -.22$, $p < .01$) and fewer days retained in treatment ($\beta = -.14$, $p < .05$). However, the latter association was moderated by participants' legal status. Nevertheless, this Spanish-translated version of the SIP (SIP-RS) appears to be a reliable and valid assessment of adverse consequences associated with alcohol and drug use, with psychometric properties comparable with the English version

Concordance Between Self-Report and Urine Drug Screen Data In Adolescent Opioid Dependent Clinical Trial Participants. Wilcox CE, Bogenschutz MP, Nakazawa M, Woody G. Addict Behav. 2013 Jun 13; 38(10): 2568-2574. [Epub ahead of print]
Objective measures of drug use are very important in treatment outcome studies of persons with substance use disorders, but obtaining and interpreting them can be challenging and not always practical. Thus, it is important to determine if, and when, drug-use self-reports are valid. To this end the authors explored the relationships between urine drug screen results and self-reported substance use among adolescents and young adults with opioid dependence participating in a clinical trial of buprenorphine-naloxone. In this study, 152 individuals seeking treatment for opioid dependence were randomized to a 2-week detoxification with buprenorphine-naloxone (DETOX) or 12weeks of buprenorphine-naloxone (BUP), each with weekly individual and group drug counseling. Urine drug screens and self-reported frequency of drug use were obtained weekly, and patients were paid $5 for completing weekly assessments. At weeks 4, 8, and 12, more extensive assessments were done, and participants were reimbursed $75. Self-report data were dichotomized (positive vs. negative), and for each major drug class the authors computed the kappa statistic and the sensitivity, specificity, positive predictive value, and negative predictive value of self-report using urine drug screens as the "gold standard". Generalized linear mixed models were used to explore the effect of treatment group assignment, compensation amounts, and participant characteristics on self-report. In general, findings supported the validity of self-reported drug use. However, those in the BUP group were more likely to under-report cocaine and opioid use. Therefore, if used alone, self-report would have magnified the treatment effect of the BUP condition.

Perceptions Of Drug Users Regarding Hepatitis C Screening and Care: A Qualitative Study. Jordan AE, Masson CL, Mateu-Gelabert P, McKnight C, Pepper N, Bouche K, Guzman L, Kletter E, Seewald RM, Des-Jarlais DC, Sorensen JL, Perlman DC. Harm Reduct J. 2013 Jun 20; 10: 10.
Illicit drug users have a high prevalence of HCV and represent the majority of newly infected persons in the U.S. Despite the availability of effective HCV treatment, few drug users have been evaluated or treated for HCV. Racial and ethnic minorities have a higher incidence and prevalence of HCV and higher HCV-related mortality. Factors contributing to poor engagement in care are incompletely understood. Fourteen mixed-gender focus groups of either African American or Latino/a drug users (N = 95) discussed barriers to HCV testing and treatment. Themes were identified through content analysis of focus group discussions. Many drug users were tested for HCV in settings where they were receiving care. Outside of these settings, most were unaware of voluntary test sites. After testing HCV positive, drug users reported not receiving clear messages regarding the meaning of a positive HCV test, the impact of HCV infection, or appropriate next steps including HCV clinical evaluations. Many drug users perceived treatment as unimportant because they lacked symptoms, healthcare providers minimized the severity of the diagnosis, or providers did not recommend treatment. Mistrust of the motivations of healthcare providers was cited as a barrier to pursuing treatment. Social networks or social interactions were a source of HCV-related information and were influential in shaping drug users perceptions of treatment and its utility. The authors conclude that drug users perceived a paucity of settings for self-initiated HCV testing and poor provider-patient communication at test sites and during medical encounters. Notably, drug users reported having an unclear understanding about the meaning of a positive HCV test, the health

implications of HCV infection, the importance of clinical evaluations and monitoring, and of treatment options for HCV. Efforts to improve the delivery of clinical messages about HCV infection for drug users at test settings and clinical encounters are needed.

Associations between Post-Traumatic Stress Symptoms, Stimulant Use, and Treatment Outcomes: A Secondary Analysis of NIDA's Women and Trauma Study. Ruglass LM, Hien DA, Hu MC, Campbell AN. Am J Addict. 2013 Jun 26. Epub ahead of print.
The objective of this study was to examine the associations between post-traumatic stress disorder (PTSD) symptoms, stimulant use, and treatment outcomes among dually diagnosed women. Participants were 141 women who participated in a multisite clinical trial of group treatments for PTSD and addictions. Generalized linear models indicated Seeking Safety (SS; a cognitive-behavioral intervention) was significantly more effective than Women's Health Education (WHE; a control group intervention) in reducing stimulant use at follow-up among women who were heavy stimulant users at pre-treatment and who showed improvements in PTSD symptoms. There were no significant differences between the interventions among women who were light stimulant users at treatment entry. These findings suggest that integrated treatment of co-occurring PTSD and addictions may be more effective than general health education approaches for heavy stimulant users. Assessment of frequency of stimulant use among individuals with PTSD symptoms may inform treatment selection for this population.

Relationship Of Age To Impulsivity and Decision Making: A Baseline Secondary Analysis Of A Behavioral Treatment Study In Stimulant Use Disorders. Kalapatapu RK, Lewis DF, Vinogradov S, Batki SL, Winhusen T. J Addict Dis. 2013; 32(2): 206-216.
Because stimulant use disorders remain prevalent across the lifespan, cognition is an important area of clinical care and research focus among aging adults with stimulant use disorders. This secondary analysis of a National Institute on Drug Abuse Clinical Trials Network study suggests that decision making, verbal learning/memory, executive function, and set shifting are important cognitive domains to screen clinically and treat in aging adults with stimulant use disorders. Some suggestions are made on how clinical treatment providers can practically use these results. An important direction for future research is the development of cognitively remediating treatments for impaired cognitive domains in aging adults with stimulant use disorders.

Intimate Partner Violence Outcomes In Women With PTSD and Substance Use: A Secondary Analysis Of NIDA Clinical Trials Network "Women and Trauma" Multi-site Study. Cohen LR, Field C, Campbell AN, Hien DA. Addict Behav. 2013 Jul; 38(7): 2325-2332. Epub 2013 Mar 21.
Studies have shown strong associations between intimate partner violence (IPV) and both posttraumatic stress disorder (PTSD) and substance use disorders (SUD). Despite these linkages, research on the dual diagnosis of PTSD-SUD and its relationship to IPV is in an early stage, and little is known about how PTSD-SUD treatment might influence IPV outcomes. The current study is a secondary analysis of a larger NIDA Clinical Trials Network study exploring the effectiveness of two behavioral interventions for women with comorbid PTSD-SUD. Participants (n=288) were randomly assigned to Seeking Safety (SS), a cognitive-behavioral treatment that focuses on trauma and substance abuse symptoms, or to Women's

Health Education, a psychoeducational group. Logistic regressions were used to examine how treatment condition, identified risk factors and their interactions were related to IPV. Results showed that participants who were abstinent at baseline were significantly less likely to experience IPV over the 12-month follow-up period, whereas participants living with someone with an alcohol problem were significantly more likely to experience IPV over follow-up. Findings also showed that at a trend level participants with recent interpersonal trauma at baseline and higher total of lifetime trauma exposures were more likely to report IPV during follow-up. Although there was no main effect for treatment condition, a significant interaction between treatment condition and baseline abstinence was found. Participants who were abstinent at baseline and in the SS condition were significantly less likely to report IPV over follow-up. These findings indicate that an integrated treatment for PTSD and SUD was associated with significantly better IPV outcomes for a subset of individuals. The possibility that women with PTSD-SUD may differentially benefit from SS has important clinical implications. Further research examining the intersection of PTSD, SUD and IPV, and the impact of treatment on a range of outcomes is needed.

Therapist Predictors Of Treatment Delivery Fidelity In A Community-Based Trial Of 12-Step Facilitation. Campbell BK, Buti A, Fussell HE, Srikanth P, McCarty D, Guydish JR. Am J Drug Alcohol Abuse. 2013 Jul 9. [Epub ahead of print].
Therapist characteristics may be associated with variation in consistency, quality and effectiveness of treatment delivery. The authors examined associations between treatment fidelity and therapist education, experience, treatment orientation and perceived skills in a randomized, multi-site trial of Twelve Step Facilitation (TSF). Raters scored audio-recorded, TSF sessions (n = 966; 97% of TSF sessions) from 32 community-based, trained therapists for adherence, competence, empathy and global session performance. Therapists with graduate degrees had significantly higher adherence and global performance fidelity ratings. Therapists reporting more positive attitudes toward 12-Step groups had lower adherence ratings. Being in recovery was associated with lower fidelity in univariate tests, but higher adherence in multivariate analysis. Fidelity was higher for therapists reporting self-efficacy in basic counseling skills and lower for self-efficacy in addiction-specific counseling skills. Fidelity was also superior in group relative to individual TSF sessions. Results have implications for therapist selection, training and supervision in community-based, effectiveness trials and community implementation of evidence-based treatments. To obtain high fidelity and improve outcomes, it may be preferable to choose masters level therapists who are open to learning new treatments and have good, general counseling skills.

Below are selected articles from the special edition of the ***Social Work in Public Health Journal*** entitled *The Role of Social Work in the Prevention and Treatment of Substance use Disorders*. This was a unique opportunity to publish a double edition of the journal on a broad range of topics related to etiology, assessment, treatment, and prevention of substance use disorders. This journal reaches a wide range of social workers and others who do not specialize in addiction.

Treatment for Substance Use Disorder: Opportunities and Challenges under the Affordable Care Act. Tai B, Volkow ND. Soc Work Public Health. 2013 May; 28(3-4): 165-174.
Addiction is a chronic brain disease with consequences that remain problematic years after discontinuation of use. Despite this, treatment models focus on acute interventions and are carved out from the main health care system. The Patient Protection and Affordable Care Act (2010) brings the opportunity to change the way substance use disorder (SUD) is treated in the United States. The treatment of SUD must adapt to a chronic care model offered in an integrated care system that screens for at-risk patients and includes services needed to prevent relapses. The partnering of the health care system with substance abuse treatment programs could dramatically expand the benefits of prevention and treatment of SUD. Expanding roles of health information technology and nonphysician workforces, such as social workers, are essential to the success of a chronic care model.

Brief Strategic Family Therapy: Engaging Drug Using/Problem Behavior Adolescents and Their Families In Treatment. Szapocznik J, Zarate M, Duff J, Muir J. Soc Work Public Health. 2013 May; 28(3-4): 206-223.
Despite the efficacy of family-based interventions for improving outcomes for adolescent behavior problems such as substance use, engaging and retaining whole families in treatment is one of the greatest challenges therapists confront. This article illustrates how the Brief Strategic Family Therapy model, a family-based, empirically validated intervention designed to treat children and adolescents' problem behaviors, can be used to increase engagement, improve retention, and bring about positive outcomes for families. Research evidence for efficacy and effectiveness is also presented.

Social Workers and Delivery Of Evidence-Based Psychosocial Treatments For Substance Use Disorders. Wells EA, Kristman-Valente AN, Peavy KM, Jackson TR. Soc Work Public Health. 2013 May; 28(3-4): 279-301.
Social workers encounter individuals with substance use disorders (SUDs) in a variety of settings. With changes in health care policy and a movement toward integration of health and behavioral health services, social workers will play an increased role vis-á-vis SUD. As direct service providers, administrators, care managers, and policy makers, they will select, deliver, or advocate for delivery of evidence-based SUD treatment practices. This article provides an overview of effective psychosocial SUD treatment approaches. In addition to describing the treatments, the article discusses empirical support, populations for whom the treatments are known to be efficacious, and implementation issues.

Blending Research and Practice: An Evolving Dissemination Strategy In Substance Abuse. Michel ME, Pintello DA, Subramaniam G. Soc Work Public Health. 2013 May; 28(3-4): 302-312.
Substance abuse is a leading cause of death and disability throughout the world. The mission of the National Institute on Drug Abuse (NIDA) is to lead the United States in bringing the power of science to bear on drug abuse and addiction. This charge has two critical components: (a) strategic support of research across a broad range of disciplines and (b) rapid, effective dissemination of research results that can improve prevention and treatment efforts, with potential to inform policy. The NIDA Clinical Trials Network and the Blending Initiative

are critical elements of this strategy, and the social work field is poised to use these resources to expand its role in the dissemination and implementation of NIDA's mission.

12-Step Interventions and Mutual Support Programs For Substance Use Disorders: An Overview. Donovan DM, Ingalsbe MH, Benbow J, Daley DC. Soc Work Public Health. 2013 May; 28(3-4): 313-332.
Social workers and other behavioral health professionals are likely to encounter individuals with substance use disorders in a variety of practice settings outside of specialty treatment. 12-Step mutual support programs represent readily available, no cost community-based resources for such individuals; however, practitioners are often unfamiliar with such programs. The present article provides a brief overview of 12-Step programs, the positive substance use and psychosocial outcomes associated with active 12-Step involvement, and approaches ranging from ones that can be utilized by social workers in any practice setting to those developed for specialty treatment programs to facilitate engagement in 12-Step meetings and recovery activities. The goal is to familiarize social workers with 12-Step approaches so that they are better able to make informed referrals that match clients to mutual support groups that best meet the individual's needs and maximize the likelihood of engagement and positive outcomes.

Substance Use Disorders and HIV/AIDS Prevention and Treatment Intervention: Research and Practice Considerations. Campbell AN, Tross S, Calsyn DA. Soc Work Public Health. 2013 May; 28(3-4): 333-348.
Social workers are often on the front lines of the HIV/AIDS epidemic delivering prevention education and interventions, offering or linking individuals to HIV testing, and working to improve treatment access, retention, and adherence, especially among vulnerable populations. Individuals with substance use disorders face additional challenges to reducing sexual and drug risk behaviors, as well as barriers to testing, treatment, and antiretroviral therapy adherence. This article presents current data on HIV transmission and research evidence on prevention and intervention with substance abusers and highlights how individual social workers can take advantage of this knowledge in practice and through adoption and implementation within organizations.

Integrated Treatment Of Substance Use and Psychiatric Disorders. Kelly TM, Daley DC. Soc Work Public Health. 2013 May; 28(3-4): 388-406.
Epidemiological studies find that psychiatric disorders, including mental disorders and substance use disorders, are common among adults and highly comorbid. Integrated treatment refers to the focus of treatment on two or more conditions and to the use of multiple treatments such as the combination of psychotherapy and pharmacotherapy. Integrated treatment for comorbidity has been found to be consistently superior compared to treatment of individual disorders with separate treatment plans. This article focuses on a review of the risks for developing comorbid disorders and the combinations of treatments that appear to be most effective for clients with particular comorbid disorders.

Substance Use Disorders and Anxiety: A Treatment Challenge For Social Workers.
Brady KT, Haynes LF, Hartwell KJ, Killeen TK. Soc Work Public Health. 2013 May; 28(3-4): 407-423.
Converging evidence from epidemiologic and treatment studies indicate that anxiety disorders and substance use disorders commonly co-occur, and the interaction is multifaceted and variable. Epidemiological studies and investigations within clinical substance abuse populations have found an association between anxiety disorders and substance use disorders. Specific anxiety disorders including generalized anxiety disorder, panic disorder, and post traumatic stress disorder have all been associated with substance use. The association with obsessive-compulsive disorder is less robust, and some research has found a negative association. The risk of nicotine dependence is significantly higher among individuals with an anxiety disorder, and conversely, smoking has been found to be associated with trait anxiety and anxiety disorders. A review of the current literature and the relationship between specific anxiety disorders and alcohol and substance use disorders is discussed in detail. This article, written for social workers in a variety of practice settings, reviews the prevalence, diagnostic, and treatment issues at the interface of substance use disorders and anxiety disorders.

Does Cultural Adaptation Have A Role In Substance Abuse Treatment? Burlew AK, Copeland VC, Ahuama-Jonas C, Calsyn DA. Soc Work Public Health. 2013 May; 28(3-4): 440-460.
The changing ethnic composition of the nation and increasing requirements to use evidence-based treatments (EBTs) challenge mental health professionals to adapt treatments and interventions to be appropriate for their clients. This article applies the available information on cultural adaptation to substance abuse. The authors' review suggests that the most common approaches for adapting substance use interventions include some combination of either community involvement in the adaptation, existing research and literature, and/or consultation from experts to adapt EBTs. The challenges facing the development of culturally adapted interventions include the need for additional research to determine which specific EBTs warrant adaptation, the responsibility of maintaining the balance between fidelity and adaptation, and the challenge of intragroup diversity.

WOMEN AND GENDER-RELATED RESEARCH

Association of Elevated Cytokines with Childhood Adversity in a Sample of Healthy Adults. Hartwell KJ, Moran-Santa Maria MM, Twal WO, Shaftman S, DeSantis SM, McRae-Clark AL, Brady KT. J Psychiatr Res. 2013 May; 47(5): 604-610.
Childhood trauma has been associated with adult stress-related disorders. However, little is known about physiologic alterations in adults with a history of early life trauma that do not have current psychiatric or medical diagnoses. In this study, the relationships between childhood adversity and cytokine and C-reactive protein (CRP) levels in healthy adults were examined. Participants included men (n = 18) and women (n = 20) who did not meet DSM-IV criteria for Axis I psychiatric disorders or any major medical illness. Cytokine and CRP levels were obtained from baseline blood samples. Subjects completed the Early Trauma Inventory Self Report (ETI-SR). The primary outcomes included serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL1-β), and CRP levels. In addition, the mean numbers of traumatic experiences (sexual, physical, emotional, general, and the summed total) were measured. Significant positive associations were found between the total ETI score and IL-6 ($p = 0.05$), IL1-β ($p < 0.05$), and TNF-α ($p = 0.01$). Significant positive correlations were found between the number of general traumas and IL1-β ($p < 0.05$), TNF-α ($p < 0.05$), and IL-6 ($p < 0.01$). Neither the total number of traumas nor any of the trauma subscales were significantly associated with CRP levels. The positive association between childhood trauma and basal cytokine levels supports the extant literature demonstrating the long-term impact of childhood trauma and stress on homeostatic systems. Importantly, this association was found in healthy adults, suggesting that these alterations may precede the development of significant stress-related psychiatric disorder or disease.

The Effects of Exogenous Progesterone on Drug Craving and Stress Arousal in Cocaine Dependence: Impact of Gender and Cue Type. Fox HC, Sofuoglu M, Morgan PT, Tuit KL, Sinha R. Psychoneuroendocrinology. 2013 Jan 29.
Exogenous progesterone has been shown to attenuate the rewarding effects of cocaine. However, its effects on provoked drug craving, stress arousal and cognitive performance has not been systematically investigated in cocaine dependent men and women. Thus, the authors conducted a double-blind placebo-controlled study assessing the efficacy of progesterone in reducing provoked drug craving, stress system arousal and improving cognitive performance in cocaine dependent men and women. Forty-two early abstinent treatment-seeking cocaine dependent individuals were randomly assigned to either daily doses of placebo (12M/9F) or micronized progesterone (12M/9F) (400mg/day), for 7 days. Under experimental conditions, all subjects were exposed to three 5-min personalized guided imagery conditions (stress, cocaine cue, relaxing), one per day, consecutively in a random, counterbalanced order. Subjective craving, mood, hypothalamic-pituitary-adrenal (HPA) and cardiovascular output, and a cognitive measure of inhibitory control (Stroop Color Word Task) were assessed pre- and post imagery. Progesterone relative to placebo significantly decreased cue-induced craving and cortisol responses and increased cue-induced ACTH. In addition, women but not men receiving progesterone reported lower ratings of negative emotion and higher ratings of relaxed mood following stress exposure. Improved Stroop performance was observed in all participants receiving progesterone, across all conditions. Progesterone was selectively effective in reducing cocaine cue-induced but not stress-related cocaine craving as well as

specific measures of the provoked arousal state. Findings suggest that progesterone's effects on drug craving and arousal are moderated by both the type of environmental cue exposure and gender.

Sex Differences in Decreased Limbic and Cortical Grey Matter Volume in Cocaine Dependence: a Voxel-Based Morphometric Study. Rando K, Tuit K, Hannestad J, Guarnaccia J, Sinha R. Addict Biol. 2013 Jan; 18(1): 147-160.
Structural neuroimaging studies have provided evidence of differences in local brain volume between cocaine-dependent and healthy control individuals. While sex differences in aetiology, course and brain dysfunction associated with chronic cocaine abuse have been previously documented, evidence of sex-specific differences in brain volume has not been examined thus far. This study examined sex-related differences in grey matter volume between cocaine-dependent and healthy control subjects using voxel-based morphometry. High-resolution T1 structural scans were obtained from 36 inpatient, treatment-engaged 3-week abstinent cocaine-dependent (CD) individuals. Fifty healthy control subjects were also scanned. Segmentation and registration were performed in SPM8, using New Segment and DARTEL, respectively. The whole-brain statistical analysis was conducted in SPM8 using random field-based cluster-size testing and family-wise error rate correction for multiple comparisons. CD patients were found to have less grey matter volume in anterior prefrontal cortex, including frontopolar and orbitofrontal cortices, and a posterior region surrounding the parietal-occipital sulcus. Female CD patients had less grey matter volume than female controls in left inferior frontal gyrus, insula, superior temporal gyrus and hippocampus. Male CD patients had less grey matter in a superior cortical region that included the precentral gyrus and the mid-cingulate. These sex differences in lower grey matter volume add to the evidence from functional neuroimaging for sex-specific differences in the neurophysiological changes associated with chronic cocaine use.

Error Processing and Gender-Shared and -Specific Neural Predictors of Relapse in Cocaine Dependence. Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CS.. Brain. 2013 Apr; 136(Pt 4): 1231-1244.
Deficits in cognitive control are implicated in cocaine dependence. Previously, combining functional magnetic resonance imaging and a stop signal task, the authors demonstrated altered cognitive control in cocaine-dependent individuals. However, the clinical implications of these cross-sectional findings and, in particular, whether the changes were associated with relapse to drug use, were not clear. In a prospective study, the authors recruited 97 treatment-seeking individuals with cocaine dependence to perform the stop signal task during functional magnetic resonance imaging and participate in follow-up assessments for 3 months, during which time cocaine use was evaluated with timeline follow back and ascertained by urine toxicology tests. Functional magnetic resonance imaging data were analysed using general linear models as implemented in Statistical Parametric Mapping 8, with the contrast 'stop error greater than stop success trials' to index error processing. Using voxel-wise analysis with logistic and Cox regressions, the authors identified brain activations of error processing that predict relapse and time to relapse. In females, decreased error-related activations of the thalamus and dorsal anterior cingulate cortex predicted relapse and an earlier time to relapse. In males, decreased error-related activations of the dorsal anterior cingulate cortex and left insula predicted relapse and an earlier time to relapse. These regional activations were

validated with data resampling and predicted relapse with an average area under the curve of 0.849 in receiver operating characteristic analyses. These findings provide direct evidence linking deficits in cognitive control to clinical outcome in a moderate-sized cohort of cocaine-dependent individuals. These results may provide a useful basis for future studies to examine how psychosocial factors interact with cognitive control to determine drug use and to evaluate the efficacy of pharmacological or behavioural treatment in remediating deficits of cognitive control in cocaine addicts.

Changes in Smoking for Adults with and without Alcohol and Drug Use Disorders: Longitudinal Evaluation in the US Population. Weinberger AH, Pilver CE, Hoff RA, Mazure CM, McKee SA. Am J Drug Alcohol Abuse. 2013 May; 39(3): 186-193.
Little is known about the smoking cessation and smoking relapse behavior of adults with alcohol use disorders (AUDs) and drug use disorders (DUDs), The current study used longitudinal data from a representative sample of the US adult population to examine changes in smoking over 3 years for men and women with and without AUD and DUD diagnoses, Participants were current or former daily cigarette smokers at Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions who completed the Wave 2 assessment 3 years later (n = 11,973; 46% female). Analyses examined the main and gender-specific effects of AUD and DUD diagnoses on smoking cessation and smoking relapse, Wave 1 current daily smokers with a current AUD (OR = .70, 95% CI = .55, .89), past AUD (OR = .73, 95% CI = .60, .89), current DUD (OR = .48, 95% CI = .31, .76), and past DUD (OR = .62, 95% CI = .49, .79) were less likely to have quit smoking at Wave 2 than those with no AUD or DUD diagnosis. Wave 1 former daily smokers with a current AUD (OR = 2.26, 95% CI = 1.36, 3.73), current DUD (OR = 7.97, 95% CI = 2.51, 25.34), and past DUD (OR = 2.69, 95% CI = 1.84, 3.95) were more likely to have relapsed to smoking at Wave 2 than those with no AUD or DUD diagnosis. The gender by diagnosis interactions were not significant. The authors conclude that current and past AUDs and DUDs were associated with a decreased likelihood of quitting smoking, while current AUDs, current DUDs, and past DUDs were associated with an increased likelihood of smoking relapse.

The Relationship of Dysthymia, Minor Depression, and Gender to Changes in Smoking for Current and Former Smokers: Longitudinal Evaluation in the U.S. Population. Weinberger AH, Pilver CE, Desai RA, Mazure CM, McKee SA. Drug Alcohol Depend. 2013 Jan 1;1 27(13): 170-176.
Although data clearly link major depression and smoking, little is known about the association between dysthymia and minor depression and smoking behavior. The current study examined changes in smoking over 3 years for current and former smokers with and without dysthymia and minor depression. Participants who were current or former daily cigarette smokers at Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions and completed the Wave 2 assessment were included in these analyses (n=11,973; 46% female). Analyses examined the main and gender-specific effects of current dysthymia, lifetime dysthymia, and minor depression (a single diagnostic category that denoted current and/or lifetime prevalence) on continued smoking for Wave 1 current daily smokers and continued abstinence for Wave 1 former daily smokers. Wave 1 current daily smokers with current dysthymia (OR=2.13, 95% CI=1.23, 3.70) or minor depression (OR=1.53, 95% CI=1.07, 2.18) were more likely than smokers without the respective diagnosis to report continued smoking at

Wave 2. Wave 1 former daily smokers with current dysthymia (OR=0.44, 95% CI=0.20, 0.96) and lifetime dysthymia (OR=0.37, 95% CI=0.15, 0.91) were less likely than those without the diagnosis to remain abstinent from smoking at Wave 2. The gender-by-diagnosis interactions were not significant, suggesting that the impact of dysthymia and minor depression on smoking behavior is similar among men and women. The authors conclude that current dysthymia and minor depression are associated with a greater likelihood of continued smoking; current and lifetime dysthymia are associated with a decreased likelihood of continued smoking abstinence.

Neural Correlates of Impulsivity in Healthy Males and Females with Family Histories of Alcoholism. Devito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD. Neuropsychopharmacology. 2013 Apr 12. [Epub ahead of print].
Individuals family-history positive (FHP) for alcoholism have increased risk for the disorder, which may be mediated by intermediate behavioral traits such as impulsivity. Given the sex differences in the risk for and clinical presentation of addictive disorders, risk for addiction may be differentially mediated by impulsivity within FHP males and females. FHP (N=28) and family-history negative (FHN, N=31) healthy, non-substance-abusing adults completed an fMRI Go/No-Go task and were assessed on impulsivity and alcohol use. Effects of family history and sex were investigated as were associations between neural correlates of impulse control and out-of-scanner measures of impulsivity and alcohol use. FHP individuals showed greater activation in the left anterior insula and inferior frontal gyrus during successful inhibitions, an effect that was driven primarily by FHP males. Higher self-reported impulsivity and behavioral discounting impulsivity, but not alcohol use measures, were associated with greater BOLD signal in the region that differentiated the FHP and FHN groups. Impulsivity factors were associated with alcohol use measures across the FHP and FHN groups. These findings are consistent with increased risk for addiction among FHP individuals being conferred through disrupted function within neural systems important for impulse control.

Gender Differences in a Clinical Trial for Prescription Opioid Dependence. McHugh RK, Devito EE, Dodd D, Carroll KM, Potter JS, Greenfield SF, Connery HS, Weiss RD. J Subst Abuse Treat. 2013 Jul; 45(1): 38-43.
Although gender differences in substance use disorders have been identified, few studies have examined gender differences in prescription drug dependence. The aim of this study was to examine gender differences in clinical characteristics and treatment outcomes in a large clinical trial for prescription opioid dependence. Despite no pre-treatment differences in opioid dependence severity, women reported significantly greater functional impairment, greater psychiatric severity, and higher likelihood of using opioids to cope with negative affect and pain than men. Women were also more likely than men to have first obtained opioids via a legitimate prescription and to use opioids via the intended route of administration. Men reported significantly more alcohol problems than women. There were no significant gender differences in medication dose, treatment retention, or opioid outcomes. Thus, despite the presence of pre-treatment gender differences in this population, once the study treatment was initiated, women and men exhibited similar opioid use outcomes.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Research Branch

Medicinal Chemistry Section

A Rhodamine-Labeled Citalopram Analogue as a High-Affinity Fluorescent Probe for the Serotonin Transporter. Zhang P, Jorgensen TJ, Loland CJ, Newman AH. Bioorg Med Chem Lett. 2013; 23: 323-326.
A novel fluorescent ligand was synthesized as a high-affinity, high specificity probe for visualizing the serotonin transporter (SERT). The rhodamine fluorophore was extended from an aniline substitution on the 5- position of the dihydroisobenzofuran ring of citalopram (2, 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile), using an ethylamino linker. The resulting rhodamine-labeled ligand 8 inhibited [3H]5-HT uptake in COS-7 cells (Ki = 225 nM) with similar potency to the tropane-based JHC 1-064 (1), but with higher specificity towards the SERT relative to the transporters for dopamine and norepinephrine. Visualization of the SERT with compound 8 was demonstrated by confocal microscopy in HEK293 cells stably expressing EGFP-SERT.

A C-Terminal PDZ Domain-Binding Sequence Is Required For Striatal Distribution of the Dopamine Transporter. Rickhag R, Hanse, FH, Sorensen G, Strandfelt KN, Andresen B, Gotfryd K, Madsen KL, Vestergaard-Klewe I, Ammendrup-Johnsen I, Eriksen J, Newman AH, Fuchtbauer E-M, Gomeza J, Woldbye DPD, Wortwein G, Gether U. Nature Communications. e-pub March 12, 2013.
The dopamine transporter mediates reuptake of dopamine from the synaptic cleft. The cellular mechanisms controlling dopamine transporter levels in striatal nerve terminals remain poorly understood. The dopamine transporters contain a C-terminal PDZ (PSD-95/ Discs-large/ZO-1) domain-binding sequence believed to bind synaptic scaffolding proteins, but its functional significance is uncertain. Here the authors demonstrate that two different dopamine transporter knock-in mice with disrupted PDZ-binding motifs (dopamine transporter-AAA and dopamine transporter.Ala) are characterized by dramatic loss of dopamine transporter expression in the striatum, causing hyperlocomotion and attenuated response to amphetamine. In cultured dopaminergic neurons and striatal slices from dopamine transporter-AAA mice, they find markedly reduced dopamine transporter surface levels and evidence for enhanced constitutive internalization. In dopamine transporter-AAA neurons, but not in wildtype neurons, surface levels are rescued in part by expression of a dominant-negative dynamin mutation (K44A). These findings suggest that PDZ-domain interactions are critical for synaptic distribution of dopamine transporter in vivo and thereby for proper maintenance of dopamine homoeostasis.

Dopamine D3 Receptors Regulate Reconsolidation Of Cocaine Memory. Yan Y, Kong H, Wu EJ, Newman AH, Xu M. Neuroscience 2013; 241: 32-40.
Memories of learned associations between the rewarding properties of drugs of abuse and environmental cues contribute to craving and relapse in humans. Disruption of reconsolidation dampens or even erases previous memories. Dopamine (DA) mediates acquisition of reward memory and drugs of abuse can pathologically change related neuronal circuits in the

mesolimbic DA system. Previous studies showed that DA D3 receptors are involved in cocaine-conditioned place preference (CPP) and reinstatement of cocaine-seeking behavior. However, the role of D3 receptors in reconsolidation of cocaine-induced reward memory remains unclear. In the present study, the authors combined genetic and pharmacological approaches to investigate the role of D3 receptors in reconsolidation of cocaine-induced CPP. They found that the mutation of the D3 receptor gene weakened reconsolidation of cocaine-induced CPP in mice triggered by a 3-minute (min) retrieval. Furthermore, treatment of a selective D3 receptor antagonist PG01037 immediately following the 3-min retrieval disrupted reconsolidation of cocaine-induced CPP in wild-type mice and such disruption remained at least one week after the 3-min retrieval. These results suggest that D3 receptors play a key role in reconsolidation of cocaine-induced CPP in mice, and that pharmacological blockade of these receptors may be therapeutic for the treatment of cocaine craving and relapse in clinical settings.

Fenobam Sulfate Inhibits Cocaine-Taking and Cocaine-Seeking Behavior In Rats. Keck TM, Yang H-J, Bi, G-H, Huang Y, Zhang H-Y, Srivastava R, Gardner EL, Newman AH, Xi Z-X. Psychopharmacology, e-pub April 25, 2013.
The metabotropic glutamate receptor subtype 5 (mGluR5) has been reported to be critically involved in drug reward and addiction. Because the mGluR5 negative allosteric modulators (NAMs) MPEP and MTEP significantly inhibit addictive-like behaviors of cocaine and other drugs of abuse in experimental animals, it has been suggested that mGluR5 NAMs may have translational potential for treatment of addiction in humans. However, neither MPEP nor MTEP have been evaluated in humans due to their off-target actions and rapid metabolism. Herein, the authors evaluate a potential candidate for translational addiction research: a new sulfate salt formulation of fenobam, a selective mGluR5 NAM that has been investigated in humans. In rats, fenobam sulfate had superior pharmacokinetics compared to the free base, with improved Cmax (maximal plasma concentration) and longer half life. Oral (p.o.) administration of fenobam sulfate (30 or 60 mg/kg) inhibited intravenous cocaine self-administration, cocaine-induced reinstatement of drug-seeking behavior and cocaine-associated contextual cue-induced cocaine-seeking behavior in rats. Fenobam sulfate also inhibited oral sucrose self-administration and sucrose-induced reinstatement of sucrose-seeking behavior, but had no effect on locomotion. This study provides additional support for the role of mGluR5 signaling in cocaine addiction and suggests that fenobam sulfate may have translational potential in medication development for the treatment of cocaine addiction in humans.

Designer Drug Research Unit

Pharmacological Examination Of Trifluoromethyl Ring-Substituted Methcathinone Analogs. Cozzi NV, Brandt SD, Daley PF, Partilla JS, Rothman RB, Tulzer A, Sitte HH, Baumann MH. Eur J Pharmacol. 2013; 699: 180-187.
Cathinones are a class of drugs used to treat various medical conditions including depression, obesity, substance abuse, and muscle spasms. Some "designer" cathinones, such as methcathinone, mephedrone, and methylone, are used nonclinically for their stimulant or entactogenic properties. Given the recent rise in nonmedical use of designer cathinones, the

authors aimed to improve understanding of cathinone pharmacology by investigating analogs of methcathinone with a CF(3) substituent at the 2-, 3-, or 4-position of the phenyl ring (TFMAPs). They compared the TFMAPs with methcathinone for effects on monoamine uptake transporter function in vitro and in vivo, and for effects on locomotor activity in rats. At the serotonin transporter (SERT), 3-TFMAP and 4-TFMAP were 10-fold more potent than methcathinone as uptake inhibitors and as releasing agents, but 2-TFMAP was both a weak uptake inhibitor and releaser. At the norepinephrine and dopamine transporters (NET and DAT), all TFMAP isomers were less potent than methcathinone as uptake inhibitors and releasers. In vivo, 4-TFMAP released 5-HT, but not dopamine, in rat nucleus accumbens and did not affect locomotor activity, whereas methcathinone increased both 5-HT and dopamine and produced locomotor stimulation. These experiments reveal that TFMAPs are substrates for the monoamine transporters and that phenyl ring substitution at the 3- or 4-position increases potency at SERT but decreases potency at NET and DAT, resulting in selectivity for SERT. The TFMAPs might have a therapeutic value for a variety of medical and psychiatric conditions and may have lower abuse liability compared to methcathinone due to their decreased DAT activity.

Age Differences In (±) 3,4-Methylenedioxymethamphetamine (MDMA)-Induced Conditioned Taste Aversions and Monoamine Levels. Cobuzzi JL, Siletti KA, Hurwitz ZE, Wetzell B, Baumann MH, Riley AL. Dev Psychobiol. e-pub Jun 15, 2013.
Preclinical work indicates that adolescent rats appear more sensitive to the rewarding effects and less sensitive to the aversive effects of abused drugs. The present investigation utilized the conditioned taste aversion (CTA) design to measure the relative aversive effects of (±)3,4-methylenedioxymethamphetamine (MDMA; 0, 1.0, 1.8, or 3.2 mg/kg) in adolescent and adult Sprague-Dawley rats. After behavioral testing was complete, monoamine and associated metabolite levels in discrete brain regions were quantified using high-performance liquid chromatography coupled to electrochemical detection (HPLC-ECD) to determine if adolescent animals displayed a different neurochemical profile than did adult animals after being exposed to subcutaneous low doses of MDMA. Adolescent rats displayed less robust MDMA-induced taste aversions than adults during acquisition and on a final two-bottle aversion test. MDMA at these doses had no consistent effect on monoamine levels in either age group, although levels did vary with age. The relative insensitivity of adolescents to MDMA's aversive effects may engender an increased vulnerability to MDMA abuse in this specific population.

Psychobiology Section

Unique Dopamine Uptake Inhibitors That Stimulate Mesolimbic Dopamine But Do Not Produce Place Conditioning Like Cocaine. Tanda G, Li S-M, Mereu M, Thomas AM, Ebbs AL, Chun LE, Tronci V, Green JL, Zou M-F, Kopajtic TA, Newman AH, Katz JL. Psychopharmacology, DOI 10.1007/s00213-013-3109-6.
The conformation of the dopamine transporter (DAT) plays a role in the effectiveness of cocaine-like and other DAT inhibitors. Cocaine-like stimulants are intolerant to DAT conformation changes having decreased potency in cells transfected with DAT constructs that face the cytosol compared to wild-type DAT. In contrast, analogs of benztropine (BZT) are among compounds that are less affected by DAT conformational change. The displacement of

radioligand binding to various mammalian CNS sites, acute stimulation of accumbens shell dopamine levels, and place conditioning in rats among cocaine and four BZT analogs with Cl substitutions on the diphenyl-ether system including two with carboalkoxy substitutions at the 2-position of the tropane ring. Binding assays confirmed high-affinity and selectivity for the DAT with the BZT analogs which also produced significant stimulation of mesolimbic dopamine efflux. Because BZT analogs produced temporal patterns of extracellular dopamine levels different from those by cocaine (3–10 mg/kg, i.p.), the place conditioning produced by BZT analogs and cocaine was compared at doses and times at which both the increase in dopamine levels and rates of increase were similar to those produced by an effective dose of cocaine. Despite this equilibration, none of the BZT analogs tested produced significant place conditioning. The present results extend previous findings suggesting that cocaine-like actions are dependent on a binding equilibrium that favors the outward conformational state of the DAT. In contrast, BZT analogs with reduced dependence on DAT conformation have reduced cocaine-like behavioral effects and may prove useful in development of medications for stimulant abuse.

Interactions Of Cocaine With Dopamine D2-Like Antagonists. Soto PL, Katz JL. Psychopharmacology 2013; 226: 393–400.
Studies investigating dopamine D2 receptor antagonism of cocaine's discriminative stimulus effects have resulted in varied effects possibly due to the use of different antagonists, species, and procedures. The present study sought to further investigate D2 antagonism of cocaine's discriminative stimulus effects using a variety of D2 antagonists and multiple doses of the antagonists in combination with cocaine. The benzamide D2 antagonists, eticlopride, raclopride, and sulpiride, and the butyrophenone D2 antagonists haloperidol and spiperone were administered alone and in combination with cocaine in squirrel monkeys trained to discriminate cocaine from saline under a fixed-ratio food reinforcement procedure. All the D2 antagonists, except haloperidol, antagonized the discriminative stimulus effects of the cocaine training dose. However, only the benzamide D2 antagonists produced significant rightward shifts in the cocaine discriminative stimulus dose–effect curve and they only did so within a narrow dose range and time after administration. In contrast, the D2 antagonists failed to antagonize the rate suppressant effects of cocaine, and in some cases, cocaine appeared to antagonize the rate-suppressant effects of the antagonists. The present results suggest (1) that D2 antagonism of cocaine's discriminative stimulus effects depends critically on the selected antagonist, antagonist dose, and time of administration, as well as how antagonism is assessed (i.e., in terms of effects on training dose or on the cocaine dose–effect curve), (2) that the maximal shift in cocaine's discriminative stimulus dose–effect curve possible with D2 antagonists under these procedures is ~two- to threefold, and (3) that different effects of cocaine are differentially sensitive to dopamine receptor antagonism.

Proposed Voltammetry & Neurochemistry Core Section

B-Arrestin 2 Knockout Mice Exhibit Sensitized Dopamine Release and Increased Reward In Response To A Low Dose Of Alcohol. Björk K, Tronci V, Thorsell A, Tanda G, Hirth N, Heilig M, Hansson AC, Sommer WH. Psychopharmacology (Berl). E-Published 2013 Jun 19. DOI 10.1007/s00213-013-3166-x.

The rewarding effects of alcohol have been attributed to interactions between opioid and dopaminergic system within the mesolimbic reward pathway. The authors have previously shown that ablation of β-arrestin 2 (Arrb2), a crucial regulator of μ-opioid receptor function, attenuates alcohol-induced hyperlocomotion and c-fos activation in the nucleus accumbens. Here, the authors further investigated the role of Arrb2 in modulating alcohol-induced dopamine (DA) release and conditioned place preference (CPP). They also assessed the functional importance of Arrb2 for μ-opioid receptor surface expression and signaling following an acute alcohol challenge. Alcohol-evoked (0.375, 0.75, and 1.5 g/kg intraperitoneally) DA release was measured by in vivo microdialysis in the shell of nucleus accumbens. Reward was assessed by the CPP paradigm. Receptor function was assessed by μ-receptor binding and [35S]GTP-γ-S autoradiography. In Arrb2 knockout mice accumbal DA levels reach maximum response at a lower dose compared to wild-type (wt) animals. In line with these results, Arrb2 knockout mice display increased CPP for alcohol as compared to wt mice. Finally, Arrb2 mutant mice display increased μ-opioid receptor signaling in the ventral and dorsal striatum and amygdala in response to a low dose of alcohol, indicating impaired desensitization mechanisms in these mice. These results show that Arrb2 modulates the response to low doses of alcohol on various levels including μ-opioid receptor signaling, DA release, and reward. They also reveal a clear dissociation between the effects of Arrb2 on psychomotor and reward behaviors.

Office of the Scientific Director

Optical Imaging Core Facility and Cell Biology of Trafficking Unit

Synaptic Plasticity Section

Neurocircuitry Of Drug Reward. Ikemoto S, Bonci A. J. Neuropharm. e-pub May 7 2013. In recent years, neuroscientists have produced profound conceptual and mechanistic advances on the neurocircuitry of reward and substance use disorders. Here, the authors provide a brief review of intracranial drug self-administration and optogenetic self-stimulation studies that identified brain regions and neurotransmitter systems involved in drug- and reward-related behaviors. Also discussed is a theoretical framework that helps to understand the functional properties of the circuitry involved in these behaviors. The circuitry appears to be homeostatically regulated and mediate anticipatory processes that regulate behavioral interaction with the environment in response to salient stimuli. That is, abused drugs or, at least, some may act on basic motivation and mood processes, regulating behavior-environment interaction. Optogenetics and related technologies have begun to uncover detailed circuit mechanisms linking key brain regions in which abused drugs act for rewarding effects.

Cortical Activation Of Accumbens Hyperolarization-Action NMDARs Mediates Aversion-Resistant Alcohol Intake. Seif T, Chang S, Simms JA, Gibb SL, Dadgar J, Chen BT, Harvey BK, Ron D, Messing RO, Bonci A. Nat Neurosci. Epub June 30, 2013. Compulsive drinking despite serious adverse medical, social and economic consequences is a characteristic of alcohol use disorders in humans. Although frontal cortical areas have been implicated in alcohol use disorders, little is known about the molecular mechanisms and

pathways that sustain aversion-resistant intake. Here, the authors show that nucleus accumbens core (NAcore) NMDA-type glutamate receptors and medial prefrontal (mPFC) and insula glutamatergic inputs to the NAcore are necessary for aversion-resistant alcohol consumption in rats. Aversion-resistant intake was associated with a new type of NMDA receptor adaptation, in which hyperpolarization-active NMDA receptors were present at mPFC and insula but not amygdalar inputs in the NAcore. Accordingly, inhibition of Grin2c NMDA receptor subunits in the NAcore reduced aversion-resistant alcohol intake. None of these manipulations altered intake when alcohol was not paired with an aversive consequence. These results identify a mechanism by which hyperpolarization-active NMDA receptors under mPFC- and insula-to-NAcore inputs sustain aversion-resistant alcohol intake.

Clinical Pharmacology and Therapeutics Branch

Treatment Section

A Randomized Investigation Of Methadone Doses At Or Over 100 Mg/Day, Combined With Contingency Management. Kennedy AP, Phillips KA, Epstein DH, Reamer DA, Schmittner J, Preston KL. Drug Alcohol Depend. 2013 Jun 1; 130(1-3): 77-84.
Methadone maintenance for heroin dependence reduces illicit drug use, crime, HIV risk, and death. Typical dosages have increased over the past few years, based on strong experimental and clinical evidence that dosages under 60 mg/day are inadequate and that dosages closer to 100mg/day produce better outcomes. However, there is little experimental evidence for the benefits of exceeding 100 mg/day, or for individualizing methadone dosages. To provide such evidence, the authors combined individualized methadone dosages over 100 mg/day with voucher-based cocaine-targeted contingency management (CM) in 58 heroin- and cocaine-dependent outpatients. Participants were randomly assigned to receive a fixed dose increase from 70 mg/day to 100mg/day, or to be eligible for further dose increases (up to 190 mg/day, based on withdrawal symptoms, craving, and continued heroin use). All dosing was double-blind. The main outcome measure was simultaneous abstinence from heroin and cocaine. Cocaine-targeted CM worked as expected to reduce cocaine use. Polydrug use (effect-size h=.30) and heroin craving (effect-size d=.87) were significantly greater in the flexible/high-dose condition than in the fixed-dose condition, with no trend toward lower heroin use in the flexible/high-dose participants. Under double-blind conditions, dosages of methadone over 100mg/day, even when prescribed based on specific signs and symptoms, were not better than 100mg/day. This counterintuitive finding requires replication, but supports the need for additional controlled studies of high-dose methadone.

Sex Differences In Cocaine/Heroin Users: Drug-Use Triggers and Craving In Daily Life. Kennedy AP, Epstein DH, Phillips KA, Preston KL. Drug Alcohol Depend. 2013 Jan 25. pii: S0376-8716(12)00501-7. doi: 10.1016/j.drugalcdep.2012.12.025. [Epub ahead of print].
Studies of sex differences have shown that men and women with drug-use disorders differ in course and outcome and in cue-induced activation of putative brain "control network" areas. The authors evaluated sex differences in daily functioning and subjective events related to drug use with ecological momentary assessment (EMA). EMA data were collected from cocaine- and heroin-using outpatients (72 men; 42 women) in methadone maintenance in 2-5

randomly prompted (RP) entries per day and in participant-initiated entries for heroin or cocaine use or craving, for up to 25 weeks. Urine drug screens were conducted three times weekly. Data were analyzed via repeated-measures logistic regression, using sex as a predictor of responses. In RP reports, women and men reported significantly different patterns of drug-cue exposure, with women significantly more likely to report having seen cocaine or been tempted to use in the past hour. Women also had higher craving after past-hour exposure to drug cues. In reports of drug use, women, compared to men, were more likely to report that they had used more cocaine than they had meant to, tended to feel guilty more often after drug use, and to have used despite trying not to use. These findings provide real-time behavioral evidence that women respond differently than men to exposure to drug cues and to drug use, consistent with laboratory and brain-imaging findings. This information may be useful for development of sex-specific treatment strategies.

Nicotine Psychopharmacology Section

The Acute Tobacco Withdrawal Syndrome Among Black Smokers. Robinson CD, Pickworth WB, Heishman SJ, Waters AJ. Psychol Addict Behav. e-pub 25 March 2013.
Black smokers have greater difficulty quitting tobacco than White smokers, but the mechanisms underlying between-race differences in smoking cessation are not clear. One possibility is that Black smokers experience greater acute withdrawal than Whites. The authors investigated whether Black (n = 104) and White smokers (n = 99) differed in abstinence-induced changes in self-report, physiological, and cognitive performance measures. Smokers not wishing to quit completed two counterbalanced experi- mental sessions. Before one session, they abstained from smoking for at least 12 hr. They smoked normally before the other session. Black smokers reported smaller abstinence-induced changes on a number of subjective measures including the total score of the 10-item Questionnaire for Smoking Urges (QSU) and the total score of the Wisconsin Smoking Withdrawal Scale (WSWS). However, on most subjective measures, and on all objective measures, there were no between-race differences in abstinence-induced change scores. Moreover, Black participants did not report lower QSU and WSWS ratings at the abstinent session, but they did experience significantly higher QSU and WSWS ratings at the nonabstinent session. Abstinence-induced changes in subjective, physiological, and cognitive measures in White smokers were similar for smokers of nonflavored and menthol-flavored cigarettes. There was no evidence that Black smokers experienced greater acute tobacco withdrawal than Whites. To the contrary, Black participants experienced smaller abstinence-induced changes in self-reported craving and withdrawal on some measures. Racial differences in smoking cessation are unlikely to be explained by acute withdrawal.

Predicting Smoking Relapse With A Multidimensional Versus A Single-Item Tobacco Craving Measure. Berlin I, Singleton EG, Heishman SJ. Drug Alcohol Depend. e-pub 23 April 2013.
Research suggests that craving is a predictor of smoking relapse. Craving can be assessed by multiple item or multifactorial scales or by single items. However, no systematic comparisons of their prognostic validity or accuracy have been published. The French versions of the 12-item Tobacco Craving Questionnaire (FTCQ-12) and the single craving item on the Minnesota

Nicotine Withdrawal Scale (MNWS) are brief, valid, and reliable self-report measures of tobacco craving. In this secondary study, the authors analyzed data from French smokers with health-related problems enrolled in the Adjustment of DOses of NIcotine in Smoking (ADONIS) cessation trial. The authors estimated prediction models for each measure and compared their ability to distinguish correctly participants who relapsed from those who did not at 1-8 weeks after their quit date.
Adjusted for all potential confounders FTCQ-12 risk score (RS; Factor 2, Expectancy plus Factor 4, Purposefulness) and MNWS craving were valid predictors of smoking relapse at endpoints measured 1-7 weeks apart. Prognostic accuracy of FTCQ-12 RS was greatest at 1-2 weeks follow-up compared to only 1 week for MNWS craving. Sensitivity for FTCQ-12 RS and MNWS craving was 85% and 53%, respectively. The authors conclude that FTCQ-12 RS suggests a relapse process involving urges and desires in anticipation of the positive benefits of smoking linked with intent and planning to smoke. Findings also suggest that FTCQ-12 RS may be a better predictor instrument for smoking relapse than MNWS craving.

Chemistry and Drug Metabolism Section

Simultaneous Quantification Of Δ(9)-Tetrahydrocannabinol, 11-Nor-9-Carboxy-Tetrahydrocannabinol, Cannabidiol And Cannabinol In Oral Fluid By Microflow-Liquid Chromatography-High Resolution Mass Spectrometry. Concheiro M, Lee D, Lendoiro E, Huestis MA. J Chromatogr A. 2013 Jul 5; 1297: 123-130.
Δ(9)-Tetrahydrocannabinol (THC) is the primary target in oral fluid (OF) for detecting cannabis intake. However, additional biomarkers are needed to solve interpretation issues, such as the possibility of passive inhalation by identifying 11-nor-9-carboxy-THC (THCCOOH), and determining recent cannabis smoking by identifying cannabidiol (CBD) and/or cannabinol (CBN). The authors developed and comprehensively validated a microflow liquid chromatography (LC)-high resolution mass spectrometry method for simultaneous quantification of THC, THCCOOH, CBD and CBN in OF collected with the Oral-Eze(®) and Quantisal™ devices. One milliliter OF-buffer solution (0.25mL OF and 0.5mL of Oral-Eze buffer, 1:3 dilution, or 0.75mL Quantisal buffer, 1:4 dilution) had proteins precipitated, and the supernatant subjected to CEREX™ Polycrom™ THC solid-phase extraction (SPE). Microflow LC reverse-phase separation was achieved with a gradient mobile phase of 10mM ammonium acetate pH 6 and acetonitrile over 10min. The authors employed a Q Exactive high resolution mass spectrometer, with compounds identified and quantified by targeted-MSMS experiments. The assay was linear 0.5-50ng/mL for THC, CBD and CBN, and 15-500pg/mL for THCCOOH. Intra- and inter-day and total imprecision were <10.8%CV and bias 86.5-104.9%. Extraction efficiency was 52.4-109.2%, process efficiency 12.2-88.9% and matrix effect ranged from -86 to -6.9%. All analytes were stable for 24h at 5°C on the autosampler. The method was applied to authentic OF specimens collected with Quantisal and Oral-Eze devices. This method provides a rapid simultaneous quantification of THCCOOH and THC, CBD, CBN, with good selectivity and sensitivity, providing the opportunity to improve interpretation of cannabinoid OF results by eliminating the possibility of passive inhalation and providing markers of recent cannabis smoking.

Motivations To Quit Cannabis Use In An Adult Non-Treatment Sample: Are They Related To Relapse? Chauchard E, Levin KH, Copersino ML, Heishman SJ, Gorelick DA. Addict Behav. 2013; 38(9): 2422-2427.

The majority of cannabis smokers who quit do so without formal treatment, suggesting that motivations to quit are an important part of cessation process. However, little is known about how motivations relate to successful quitting. A convenience sample of 385 non-treatment-seeking adult cannabis smokers (58% male, age 16-64years at start of quit attempt) who made a "serious" (self-defined) quit attempt without formal treatment while not in a controlled environment were administered the 176-item Marijuana Quit Questionnaire (MJQQ) to assess their motivations to quit and outcome of the quit attempt. Exploratory factor analysis was performed to identify significant motivational factors. Subgroup comparisons used t-tests and ANOVA. Cox proportional hazard regression and the General Linear Model were performed to evaluate the influence of motivational factors, gender, and age on relapse status at time of interview and risk of relapse over time, with time between quit attempt and interview as a covariate. Exploratory factor analysis identified 6 motivational factors with eigenvalues >1 which accounted for 58.4% of the total variance: self-image and self-control, health concerns, interpersonal relationship concerns, legal concerns, social acceptability concerns, and self-efficacy. Women were more likely than men to be motivated by self-image/self-control, health concerns, and social acceptability concerns. Older individuals were more likely to be motivated by health concerns. At the time of interview, 339 subjects had relapsed. Self-image and self-control, health concerns, interpersonal relationship concerns, and social acceptability concerns were associated with greater likelihood of abstinence at the study interview. Legal concerns and social acceptability concerns were associated with significantly lower hazard ratios (0.88, 0.83) for relapse during the abstinent period. These findings show gender and age differences in motivations to quit cannabis smoking and that adult cannabis smokers have motivations to quite similar to those of adolescent cannabis smokers and of adults who quit alcohol and tobacco use without formal treatment. The findings suggest areas of focus to improve secondary prevention and psychosocial treatment efforts.

In Vitro Stability Of Free and Glucuronidated Cannabinoids In Blood and Plasma Following Controlled Smoked Cannabis. Scheidweiler KB, Schwope DM, Karschner EL, Desrosiers NA, Gorelick DA, and Huestis MA. Clin Chem. e-pub March 13, 2013.

Blood and plasma cannabinoid stability is important for test interpretation, and is best studied in authentic rather than fortified samples. Low and high blood and plasma pools were created for each of 10 participants after smoking a cannabis cigarette. The stabilities of Δ9-Tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), cannabidiol (CBD), cannabinol (CBN), THC-glucuronide, and THCCOOH-glucuronide were determined after 1 week at room temperature (RT), 1, 2, 4, 12 and 26±2 weeks at 4˚C and 1, 2, 4, 12, 26±2 and 52±4 weeks at -20˚C. Stability was assessed by Friedman's test. Numbers of THC-glucuronide and CBD positive blood samples were insufficient to assess stability. In blood, 11-OH-THC and CBN were stable for 1 week at RT, while THC and THCCOOH-glucuronide decreased and THCCOOH increased. In blood at 4˚C, THC, THCCOOH-glucuronide, THCCOOH, 11-OH-THC and CBN were stable for 12, 4, 4, 12 and 26 weeks, respectively, and for 12, 12, 26, 26 and 52 weeks, respectively, at -20˚C. In plasma, THC-glucuronide, THC, CBN and CBD were stable for 1 week RT, while THCCOOH-glucuronide and 11-OH-THC decreased and THCCOOH increased. In plasma at

4˚C, THC-glucuronide, THC, THCCOOH-glucuronide, THCCOOH, 11-OH-THC, CBN and CBD were stable for 26, 26, 2, 2, 26, 12 and 26 weeks, respectively, and for 52, 52, 26, 26, 52, 52 and 52 weeks, respectively, at -20˚C. Blood and plasma samples should be stored at -20˚C for no more than 3 and 6 months, respectively, to assure accurate cannabinoid quantitative results.

11-nor-9-carboxy-Δ9-Tetrahydrocannabinol Quantification In Human Oral Fluid By Liquid Chromatography-Tandem Mass Spectrometry. Scheidweiler KB, Himes SK, Chen X, Liu H-F, Huestis MA. Anal Bioanal Chem. 2013; 405(18): 6019-6027.
Currently, Δ9-tetrahydrocannabinol (THC) is the analyte quantified for oral fluid cannabinoid monitoring. The potential for false positive oral fluid cannabinoid results from passive exposure to THC-laden cannabis smoke raises concerns for this promising new monitoring technology. Oral fluid 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH) is proposed as a marker of cannabis intake since it is not present in cannabis smoke and was not measureable in oral fluid collected from subjects passively exposed to cannabis. THCCOOH concentrations are in the pg/mL range in oral fluid and pose considerable analytical challenges. A liquid chromatography tandem mass spectrometry method was developed and validated for quantifying THCCOOH in 1 mL Quantisal-collected oral fluid. After solid phase extraction, chromatography was performed on a Kinetex C18 column with a gradient of 0.01% acetic acid in water and 0.01% acetic acid in methanol with a 0.5 mL/min flow rate. THCCOOH was monitored in negative mode electrospray ionization and multiple reaction monitoring mass spectrometry. THCCOOH linear range was 12-1020 pg/mL (R2>0.995). Mean extraction efficiencies and matrix effects evaluated at low and high quality control (QC) concentrations were 40.8-65.1% and -2.4-11.5%, respectively (n=10). Analytical recoveries (bias) and total imprecision at low, mid and high QCs were 85.0-113.3% and 6.6-8.4% coefficient of variation, respectively (n=20). This is the first oral fluid THCCOOH LCMSMS triple quadrupole method not requiring derivatization to achieve a <15 pg/mL limit of quantification. The assay is applicable for workplace, driving under the influence of drugs, drug treatment, and pain management testing.

A Test Of the Cognitive Self-Medication Hypothesis Of Tobacco Smoking In Schizophrenia. Hahn B, Harvey AN, Concheiro-Guisan M, Huestis MA, Holcomb HH, Gold JM. Biol Psychiatry. 2013, May 6.
Heavier tobacco smoking among people with schizophrenia (SCZ) has been suggested to reflect self-medication of cognitive deficits. The idea that cognitive-enhancing effects of nicotine are a primary motivator of tobacco consumption in SCZ and that abstinence would deprive SCZ of such beneficial effects might explain hesitation among providers to pursue smoking cessation in SCZ. This study tested predictions of the cognitive self-medication hypothesis. In three counterbalanced sessions, 17 SCZ and 17 healthy control subjects (HCS), all smokers, were tested under ad libitum smoking or 3.5 hours after abstaining and receiving a nicotine (14 mg/24 hours) or placebo patch.
Attention task performance was improved by transdermal nicotine relative to placebo, with intermediate performance by ad libitum smoking. These effects were of similar size in SCZ and HCS and did not reflect remediation of functions disproportionately impaired in SCZ. Although more SCZ reported that the need to concentrate influenced their smoking, this was not reflected by the actual behavior of these patients. Self-reported ability to concentrate

changed with nicotine status in HCS but not SCZ, suggesting insensitivity of SCZ to nicotine-derived performance benefits. Nicotine plasma concentrations after ad libitum smoking were not associated with performance benefits but instead with the propensity to experience nicotine withdrawal upon abstinence. This association was seen selectively in SCZ, suggesting a possible reason for heavier smoking. These findings suggest that subjective or objective attentional benefits are unlikely the primary driving force of tobacco consumption in SCZ and should not discourage providers from supporting quit attempts.

Impact Of Enzymatic and Alkaline Hydrolysis On CBD Concentration In Urine.
Bergamaschi MM, Barnes A, Queiroz RH, Hurd YL, Huestis MA. Anal Bioanal Chem. 2013 May; 405(14): 4679-4689.
A sensitive and specific analytical method for cannabidiol (CBD) in urine was needed to define urinary CBD pharmacokinetics after controlled CBD administration, and to confirm compliance with CBD medications including Sativex-a cannabis plant extract containing 1:1 Δ(9)-tetrahydrocannabinol (THC) and CBD. Non-psychoactive CBD has a wide range of therapeutic applications and may also influence psychotropic smoked cannabis effects. Few methods exist for the quantification of CBD excretion in urine, and no data are available for phase II metabolism of CBD to CBD-glucuronide or CBD-sulfate. The authors optimized the hydrolysis of CBD-glucuronide and/or -sulfate, and developed and validated a GC-MS method for urinary CBD quantification. Solid-phase extraction isolated and concentrated analytes prior to GC-MS. Method validation included overnight hydrolysis (16 h) at 37 °C with 2,500 units β-glucuronidase from Red Abalone. Calibration curves were fit by linear least squares regression with 1/x (2) weighting with linear ranges ($r(2) > 0.990$) of 2.5-100 ng/mL for non-hydrolyzed CBD and 2.5-500 ng/mL for enzyme-hydrolyzed CBD. Bias was 88.7-105.3 %, imprecision 1.4-6.4 % CV and extraction efficiency 82.5-92.7 % (no hydrolysis) and 34.3-47.0 % (enzyme hydrolysis). Enzyme-hydrolyzed urine specimens exhibited more than a 250-fold CBD concentration increase compared to alkaline and non-hydrolyzed specimens. This method can be applied for urinary CBD quantification and further pharmacokinetics characterization following controlled CBD administration.

Oral Fluid and Plasma 3,4-Methylenedioxymethamphetamine (MDMA) and Metabolite Correlation After Controlled Oral MDMA Administration. Desrosiers NA, Barnes AJ, Hartman RL, Scheidweiler KB, Kohlbrich-Spargo EA, Gorelick DA, Goodwin RS, Huestis MA. Anal Bioanal Chem. 2013 May; 405(12): 4067-4076.
Oral fluid (OF) offers a noninvasive sample collection for drug testing. However, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) in OF has not been adequately characterized in comparison to plasma. The authors administered oral low-dose (1.0 mg/kg) and high-dose (1.6 mg/kg) MDMA to 26 participants and collected simultaneous OF and plasma specimens for up to 143 h after dosing. They compared OF/plasma (OF/P) ratios, time of initial detection (t first), maximal concentrations (C max), time of peak concentrations (t max), time of last detection (t last), clearance, and 3,4-methylenedioxyamphetamine (MDA)-to-MDMA ratios over time. For OF MDMA and MDA, C max was higher, t last was later, and clearance was slower compared to plasma. For OF MDA only, t first was later compared to plasma. Median (range) OF/P ratios were 5.6 (0.1-52.3) for MDMA and 3.7 (0.7-24.3) for MDA. OF and plasma concentrations were weakly but significantly correlated (MDMA: $R(2) = 0.438$, MDA: $R(2) = 0.197$, $p < 0.0001$). Median OF/P ratios were significantly higher

following high dose administration: MDMA low = 5.2 (0.1-40.4), high = 6.0 (0.4-52.3, $p < 0.05$); MDA low = 3.3 (0.7-17.1), high = 4.1 (0.9-24.3, $p < 0.001$). There was a large inter-subject variation in OF/P ratios. The MDA/MDMA ratios in plasma were higher than those in OF ($p < 0.001$), and the MDA/MDMA ratios significantly increased over time in OF and plasma. The MDMA and MDA concentrations were higher in OF than in plasma. OF and plasma concentrations were correlated, but large inter-subject variability precludes the estimation of plasma concentrations from OF.

Cortisol Reactivity In Two-Year-Old Children Prenatally Exposed To Methamphetamine. Kirlic N, Newman E, Lagasse LL, Derauf C, Shah R, Smith LM, Arria AM, Huestis MA, Haning W, Strauss A, Dellagrotts S, Dansereau LM, Abar B, Neal CR, Lester BM. J Study Alcohol Drugs. 2013 May; 74(3): 447-451.
Until now, the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in children with prenatal methamphetamine exposure (PME) had been unexamined. Previous research indicates that prenatal exposure to stimulant drugs is associated with dose-response alterations in neural growth and connectivity and consequent neurobehavioral deficits. In addition, children of drug-using parents are at an increased risk for exposure to chronic postnatal stress. In this preliminary study, the authors examined the associations of PME and postnatal environmental stress with cortisol stress reactivity in children with PME. Participants were 2-year-old children (N = 123; 55.3% male) with PME from a multicenter longitudinal Infant, Development, Environment, and Lifestyle Study. Saliva samples were obtained before and after a stress-inducing separation task. Hierarchical multiple regression analyses examined prenatal drug exposure, methodological and postnatal stress covariates, and interactions between levels of PME and postnatal stress. Mild to moderate potential for child physical abuse moderated increased cortisol reactivity in high exposed children with PME. Blunted cortisol reactivity was associated with caregiver's postnatal alcohol use, child's behavioral dysregulation, and the interaction between higher levels of PME and caregiver's psychopathology. Consistent with the known effects of stimulant drugs and chronically stressful environments on the HPA axis and, thus, the toxic stress and allostatic load phenomena, our results imply that elevated PME may be associated with alterations in the programming of the HPA axis reflecting hyperactivity, which under significant and chronic environmental stress then may become hypoactive.

Changes In Smoking Patterns During Pregnancy. Eiden RD, Homish GG, Colder CR, Schuetze P, Gray TR, Huestis MA. Subs Use Misuse. 2013 May; 48(7): 513-522.
This study examined trajectories of smoking during pregnancy among low-income smokers and differences on demographics, psychopathology, and smoking outcome expectancies among women with different smoking trajectories. The sample consisted of 215 urban pregnant smokers living in the United States. Results indicated four trajectories of smoking and significant changes over time within each trajectory. Persistent smokers had the highest demographic and mental health risks, reported higher craving compared to light smokers, and were more likely to endorse smoking to reduce negative affect, for state enhancement motives. Implications for intervention are discussed.

Qualitative Confirmation Of 9 Synthetic Cannabinoids and 20 Metabolites In Human Urine Using LC-MS/MS and Library Search. Wohlfarth A, Scheidweiler KB, Chen X, Liu HF, Huestis MA. Anal Chem. 2013 Apr 2; 85(7): 3730-3738.
Synthetic cannabinoids are an emerging illicit drug class. The variety of available substances is large and ever-changing, making it difficult for laboratories to remain current. The authors present a qualitative LC-MS/MS method identifying urinary metabolites of JWH-018, JWH-073, JWH-081, JWH-122, JWH-200, JWH-210, JWH-250, RCS-4, and AM2201 and the parent compounds JWH-018, JWH-073, JWH-081, JWH-122, JWH-210, JWH-250, RCS-4, AM2201, and MAM2201. After enzymatic hydrolysis, urinary proteins were precipitated with acetonitrile. Chromatography utilized a 10 min gradient on a Kinetex XB-C18 column with 0.1% formic acid in water and acetonitrile. Scheduled multiple reaction monitoring "survey scans" were followed by information-dependent acquisition-enhanced product ion scan experiments on an ABSciex 5500 QTRAP mass spectrometer. Analytes were identified by software-assisted library searching against reference spectra. The method was fully validated, including proof of selectivity (no exogenous or endogenous interferences were observed), assessment of matrix effects (95-122%) and recovery (53-95%), determination of limits of detection (0.5-10 ng/mL), carry-over studies (thresholds between 100 and 1000 ng/mL), and determination of autosampler stability (samples were stable for at least 3 days). Hydrolysis efficiency was thoroughly investigated for a wide range of glucuronides and for the reference standard, JWH-018 5-hydroxypentyl glucuronide.

Metabolic Effects Of Chronic Cannabis Smoking. Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, Courville A, Hall G, Chen KY, Volkow ND, Kunos G, Huestis MA, Skarulis MC. Diabetes Care. 2013, Mar 25.
The authors examined if chronic cannabis smoking is associated with hepatic steatosis, insulin resistance, reduced β-cell function, or dyslipidemia in healthy individuals. In a cross-sectional, case-control study, they studied cannabis smokers (n = 30; women, 12; men, 18; 27 ± 8 years) and control subjects (n = 30) matched for age, sex, ethnicity, and BMI (27 ± 6). Abdominal fat depots and intrahepatic fat content were quantified by magnetic resonance imaging and proton magnetic resonance spectroscopy, respectively. Insulin-sensitivity indices and various aspects of β-cell function were derived from oral glucose tolerance tests (OGTT). Self-reported cannabis use was: 9.5 (2-38) years; joints/day: 6 (3-30) [median (range)]. Carbohydrate intake and percent calories from carbohydrates, but not total energy intake, were significantly higher in cannabis smokers. There were no group differences in percent total body fat, or hepatic fat, but cannabis smokers had a higher percent abdominal visceral fat (18 ± 9 vs. 12 ± 5%; P = 0.004). Cannabis smokers had lower plasma HDL cholesterol (49 ± 14 vs. 55 ± 13 mg/dL; P = 0.02), but fasting levels of glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, or free fatty acids (FFA) were not different. Adipocyte insulin resistance index and percent FFA suppression during an OGTT was lower (P < 0.05) in cannabis smokers. However, oral glucose insulin sensitivity index, measures of β-cell function, or incretin concentrations did not differ between the groups. Chronic cannabis smoking was associated with visceral adiposity and adipose tissue insulin resistance but not with hepatic steatosis, insulin insensitivity, impaired pancreatic β-cell function, or glucose intolerance.

Integrative Neuroscience Branch

Structural Biology Unit

Rapid Sensitization Of Physiological, Neuronal, and Locomotor Effects Of Nicotine: Critical Role Of Peripheral Drug Actions. Lenoir M, Tang J, Woods AS, and Kiyatkin E. Journal of Neuroscience 2013; 33(24): 9937–9949.
Repeated exposure to nicotine and other psychostimulant drugs produces persistent increases in their psychomotor and physiological effects (sensitization), a phenomenon related to the drugs' reinforcing properties and abuse potential. Here the authors examined the role of peripheral actions of nicotine in nicotine-induced sensitization of centrally mediated physiological parameters (brain, muscle, and skin temperatures), cortical and VTA EEG, neck EMG activity, and locomotion in freely moving rats. Repeated injections of intravenous nicotine (30µg/kg) induced sensitization of the drug's effects on all these measures. In contrast, repeated injections of the peripherally
acting analog of nicotine, nicotine pyrrolidine methiodide (nicotinePM, 30µg/kg, i.v.) resulted in habituation (tolerance) of the same physiological, neuronal, and behavioral measures. However, after repeated nicotine exposure, acute nicotinePM injections induced nicotine-like physiological responses: powerful cortical and VTA EEG desynchronization, EMG activation, a large brain temperature increase, but weaker hyperlocomotion. Additionally, both the acute locomotor response to nicotine and nicotine-induced locomotor sensitization were attenuated by blockade of peripheral nicotinic receptors by hexamethonium (3 mg/kg, i.v.). These data suggest that the peripheral actions of nicotine, which precede its direct central actions, serve as a conditioned interoceptive cue capable of eliciting nicotine-like physiological and neural responses after repeated nicotine exposure. Thus, by providing a neural signal to the CNS that is repeatedly paired with the direct central effects of nicotine, the drug's peripheral actions play a critical role in the development of nicotine-induced physiological, neural, and behavioral sensitization.

A New Interpretative Paradigm For Conformational Protein Diseases. Agnati LF, Guidolin D, Ciruela F, Carone C, Vallelunga A, Escuela DO, Woods AS, Genedani S, Fuxe K. Current Protein and Peptide Science 2013; 14(2): 141-160.
Conformational Protein Diseases (CPDs) comprise over forty clinically and pathologically diverse disorders in which specific altered proteins accumulate in cells or tissues of the body. The most studied are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion diseases, inclusion body myopathy, and the systemic amyloidoses. They are characterized by three dimensional conformational alterations, which are often rich in β-structure. Proteins in this non-native conformation are highly stable, resistant to degradation, and have an enhanced tendency to aggregate with like protein molecules. The misfolded proteins can impart their anomalous properties to soluble, monomeric proteins with the same amino acid sequence by a process that has been likened to seeded crystallization. However, these potentially pathogenic proteins also have important physiological actions, which have not completely characterized. This opens up the question of what process transforms physiological actions into pathological actions and most intriguing, is why potentially dangerous proteins have been maintained during evolution and are present from yeasts to humans. In the present paper, the authors introduce the concept of mis-

exaptation and of mis-tinkering since they may help in clarifying some of the double edged sword aspects of these proteins. Against this background an original interpretative paradigm for CPDs will be given in the frame of the previously proposed Red Queen Theory of Aging.

Molecular Neuropsychiatry Research Branch

CREB Phosphorylation Regulates Striatal Transcriptional Responses In the Self-Administration Model Of Methamphetamine Addiction in the Rat. Krasnova IN, Chiflikyan M, Justinova Z, McCoy MT, Ladenheim B, Jayanthi S, Quintero C, Brannock C, Barnes C, Adair JE, Lehrmann E, Kobeissy FH, Gold MS, Becker KG, Goldberg SR, Cadet JL. Neurobiol Dis. 58C:132-143. Epub May 2013.

Neuroplastic changes in the dorsal striatum participate in the transition from casual to habitual drug use and might play a critical role in the development of methamphetamine (METH) addiction. The authors examined the influence of METH self-administration on gene and protein expression that may form substrates for METH-induced neuronal plasticity in the dorsal striatum. Male Sprague-Dawley rats self-administered METH (0.1mg/kg/injection, i.v.) or received yoked saline infusions during eight 15-h sessions and were euthanized 2h, 24h, or 1month after cessation of METH exposure. Changes in gene and protein expression were assessed using microarray analysis, RT-PCR and Western blots. Chromatin immunoprecipitation (ChIP) followed by PCR was used to examine epigenetic regulation of METH-induced transcription. METH self-administration caused increases in mRNA expression of the transcription factors, c-fos and fosb, the neurotrophic factor, Bdnf, and the synaptic protein, synaptophysin (Syp) in the dorsal striatum. METH also caused changes in ΔFosB, BDNF and TrkB protein levels, with increases after 2 and 24h, but decreases after 1month of drug abstinence. Importantly, ChIP-PCR showed that METH self-administration caused enrichment of phosphorylated CREB (pCREB), but not of histone H3 trimethylated at lysine 4 (H3K4me3), on promoters of c-fos, fosb, Bdnf and Syp at 2h after cessation of drug intake. These findings show that METH-induced changes in gene expression are mediated, in part, by pCREB-dependent epigenetic phenomena. Thus, METH self-administration might trigger epigenetic changes that mediate alterations in expression of genes and proteins serving as substrates for addiction-related synaptic plasticity.

Chronic Co-Administration Of Nicotine and Methamphetamine Causes Differential Expression Of Immediate Early Genes In the Dorsal Striatum and Nucleus Accumbens Of Rats. Saint-Preux F, Bores LR, Tulloch I, Ladenheim B, Kim R, Thanos PK, Volkow ND, Cadet JL. Neuroscience. 2013 Jul 23; 243: 89-96. Epub Apr 2013.

Nicotine and methamphetamine (METH) cause addiction by triggering neuroplastic changes in brain reward pathways though they each engage distinct molecular targets (nicotine receptors and dopamine transporters respectively). Addiction to both drugs is very prevalent, with the vast majority of METH users also being smokers of cigarettes. This co-morbid occurrence thus raised questions about potential synergistic rewarding effects of the drugs. However, few studies have investigated the chronic neurobiological changes associated with co-morbid nicotine and METH addiction. Here the authors investigated the effects of these two drugs alone and in combination on the expression of several immediate early genes (IEGs) that are sensitive to drug exposures. Chronic exposure to either nicotine or METH caused significant

decreases in the expression of fosb, fra1, and fra2 in the nucleus accumbens (NAc) but not in the dorsal striatum whereas the drug combination increased fra2 expression in both structures. Except for junB mRNA levels that were decreased by the three drug treatments in the NAc, there were no significant changes in the Jun family members. Of the Egr family members, NAc egr2 expression was decreased after nicotine and the drug combination whereas NAc egr3 was decreased after METH and the drug combination. The drug combination also increased striatal egr3 expression. The Nr4a family member, nr4a2/nurr1, showed increased striatal expression after all three drug treatments, while striatal nr4a3/nor-1 expression was increased by the drug combination whereas NAc nr4a1/nurr77 was decreased by nicotine and the drug combination. These observations suggest that, when given in combination, the two drugs exert distinct effects on the expression of IEGs in dopaminergic projection areas from those elicited by each drug alone. The significance of these changes in IEG expression and in other molecular markers in fostering co-morbid METH and nicotine abuse needs to be further evaluated.

Chemical Biology Research Branch

Drug Design and Synthesis Section

Liposomes Containing Monophosphoryl Lipid A: A Potent Adjuvant System For Inducing Antibodies To Heroin Hapten Analogs. Matyas GR, Mayorov AV, Rice KC, Jacobson AE, Cheng K, Iyer MR, Li F, Janda KD, Alving CR. Vaccine 2013; 31(26): 2804-2810.

In order to create an effective immunization approach for a potential vaccine to heroin, liposomes containing monophosphoryl lipid A [L(MPLA)] were tested as an adjuvant system to induce antibodies to heroin hapten analogs. Four synthetic haptens and two immunization strategies were employed. In the first strategy, a hydrophobic 23 amino acid immunogenic peptide derived from the membrane proximal external region of gp41 from HIV-1 envelope protein was embedded as a carrier in the outer surface of L(MPLA), to which was conjugated a 15 amino acid universal T cell epitope and a terminal heroin hapten analog. In the second strategy, tetanus toxoid (TT) carrier protein was decorated with haptens by conjugation, and the hapten-conjugated protein was mixed with L(MPLA). After immunization of mice, each of the immunization strategies was effective for induction of IgG anti-hapten antibodies. The first immunization strategy induced a mean end-point IgG titer against one of two haptens tested of approximately 12,800; however, no detectable antibodies were induced against the liposome-associated HIV-1 carrier peptide. In the second immunization strategy, depending on the hapten used for decorating the TT, end-point IgG titers ranged from 100,000 to 6,500,000. In this strategy, in which hapten was conjugated to the TT, end-point IgG titers of 400,000 to the TT carrier were observed with each conjugate. However, upon mixing unconjugated TT with L(MPLA), anti-TT titers of 6,500,000 were observed. The authors conclude that L(MPLA) serves as a potent adjuvant for inducing antibodies to candidate heroin haptens. However, antibodies to the carrier peptide or protein were partly or completed inhibited by the presence of conjugated hapten.

Epidermal Adrenergic Signaling Contributes To Inflammation and Pain Sensitization in a Rat Model Of Complex Regional Pain Syndrome. Li W, Shi X, Wang L, Guo T, Wei T, Cheng K, Rice KC, Kingery WS, Clark JD. Pain 2013; 154(8): 1224-1236.
In many patients, the sympathetic nervous system supports pain and other features of complex regional pain syndrome (CRPS). Accumulating evidence suggests that interleukin (IL)-6 also plays a role in CRPS, and that catecholamines stimulate production of IL-6 in several tissues. The authors hypothesized that norepinephrine acting through specific adrenergic receptors expressed on keratinocytes stimulates the production of IL-6 and leads to nociceptive sensitization in a rat tibial fracture/cast model of CRPS. Their approach involved catecholamine depletion using 6-hydroxydopamine or, alternatively, guanethidine, to explore sympathetic contributions. Both agents substantially reduced nociceptive sensitization and selectively reduced the production of IL-6 in skin. Antagonism of IL-6 signaling using TB-2-081 also reduced sensitization in this model. Experiments using a rat keratinocyte cell line demonstrated relatively high levels of β2-adrenergic receptor (β2-AR) expression. Stimulation of this receptor greatly enhanced IL-6 expression when compared to the expression of IL-1β, tumor necrosis factor (TNF)-α, or nerve growth factor. Stimulation of the cells also promoted phosphorylation of the mitogen-activated protein kinases P38, extracellular signal-regulated kinase, and c-Jun amino-terminal kinase. Based on these in vitro results, we returned to animal testing and observed that the selective β2-AR antagonist butoxamine reduced nociceptive sensitization in the CRPS model, and that local injection of the selective β2-AR agonist terbutaline resulted in mechanical allodynia and the production of IL-6 in the cells of the skin. No increases in IL-1β, TNF-α, or nerve growth factor levels were seen, however. These data suggest that in CRPS, norepinephrine released from sympathetic nerve terminals stimulates β2-ARs expressed on epidermal keratinocytes, resulting in local IL-6 production, and ultimately, pain sensitization.

Probes For Narcotic Receptor Mediated Phenomena. 47. Novel C4a- and N-Substituted-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-C]Pyridin-6-Ols. Iyer MR, Rothman RB, Dersch CM, Jacobson AE, Rice KC. Bioorg Med Chem. 2013; 21(11): 3298-3309.
A series of N-methyl rac-cis-4a-aralkyl- and alkyl-substituted-1,2,3,4,4a,9a-hexahydrobenzofuro [2,3-c]pyridin-6-ols have been prepared (2a–l) using a simple previously designed synthetic route, in order to find a ligand that would interact with both μ- and δ-opioid receptors. A C4a-phenethyl derivative 2a, was found to have modest receptor affinity both at μ- (Ki = 60 nM) and δ-opioid receptors (Ki = 64 nM). The N-methyl substituent of 2a and that of other ligands in the series was then modified to obtain compounds with different N-substituents that might provide higher affinity at both receptors. A number of compounds differently substituted at C4a and N were synthesized and evaluated. Binding studies and functional assays revealed a moderately selective δ-antagonist (2l), selective μ–δ antagonists (3d, 3g), and a μ–κ antagonist (3f).

CRF–CRF1 Receptor System in the Central and Basolateral Nuclei of the Amygdala Differentially Mediates Excessive Eating of Palatable Food. Lemolo A, Blasio A, St Cyr SA, Jiang F, Rice KC, Sabino V, Cottone P. Neuropsychopharm. 2013. Epub ahead of print.
Highly palatable foods and dieting are major contributing factors for the development of compulsive eating in obesity and eating disorders. The authors previously demonstrated that intermittent access to palatable food results in corticotropin-releasing factor-1 (CRF1) receptor

antagonist-reversible behaviors, which include excessive palatable food intake, hypophagia of regular chow, and anxiety-like behavior. However, the brain areas mediating these effects are still unknown. Male Wistar rats were either fed chow continuously for 7 days/week (Chow/Chow group), or fed chow intermittently 5 days/week, followed by a sucrose, palatable diet 2 days/week (Chow/Palatable group). Following chronic diet alternation, the effects of microinfusing the CRF1 receptor antagonist R121919 (0, 0.5, 1.5 μg/side) in the central nucleus of the amygdala (CeA), the basolateral nucleus of the amygdala (BlA), or the bed nucleus of the stria terminalis (BNST) were evaluated on excessive intake of the palatable diet, chow hypophagia, and anxiety-like behavior. Furthermore, CRF immunostaining was evaluated in the brain of diet cycled rats. Intra-CeA R121919 blocked both excessive palatable food intake and anxiety-like behavior in Chow/Palatable rats, without affecting chow hypophagia. Conversely, intra-BlA R121919 reduced the chow hypophagia in Chow/Palatable rats, without affecting excessive palatable food intake or anxiety-like behavior. Intra-BNST treatment had no effect. The treatments did not modify the behavior of Chow/Chow rats. Immunohistochemistry revealed an increased number of CRF-positive cells in CeA—but not in BlA or BNST—of Chow/Palatable rats, during both withdrawal and renewed access to the palatable diet, compared with controls. These results provide functional evidence that the CRF–CRF1 receptor system in CeA and BlA has a differential role in mediating maladaptive behaviors resulting from palatable diet cycling. CRF–CRF1 receptor system in the central and basolateral nuclei of the amygdala differentially mediates excessive eating of palatable food.

The HIV Antiretroviral Drug Efavirenz Has LSD-Like Properties. Gatch MB, González MJ, Huang RQ, Yang W, Kozlenkov A, Nguyen JD, Rice KC, France C P, Dillon GH, Forster MJ, Schetz JA. Neuropsychopharmacol. 2013. Epub ahead of print.
Anecdotal reports have surfaced concerning misuse of the HIV antiretroviral medication efavirenz ((4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one) by HIV patients and non-infected teens who crush the pills and smoke the powder for its psychoactive effects. Molecular profiling of the receptor pharmacology of efavirenz pinpointed interactions with multiple established sites of action for other known drugs of abuse including catecholamine and indolamine transporters, and GABAA and 5-HT2A receptors. In rodents, interaction with the 5-HT2A receptor, a primary site of action of lysergic acid diethylamine (LSD), appears to dominate efavirenz's behavioral profile. Both LSD and efavirenz reduce ambulation in a novel open-field environment. Efavirenz occasions drug-lever responding in rats discriminating LSD from saline, and this effect is abolished by selective blockade of the 5-HT2A receptor. Similar to LSD, efavirenz induces head-twitch responses in wild-type, but not in 5-HT2A-knockout, mice. Despite having GABAA-potentiating effects (like benzodiazepines and barbiturates), and interactions with dopamine transporter, serotonin transporter, and vesicular monoamine transporter 2 (like cocaine and methamphetamine), efavirenz fails to maintain responding in rats that self-administer cocaine, and it fails to produce a conditioned place preference. Although its molecular pharmacology is multifarious, efavirenz's prevailing behavioral effect in rodents is consistent with LSD-like activity mediated via the 5-HT2A receptor. This finding correlates, in part, with the subjective experiences in humans who abuse efavirenz and with specific dose-dependent adverse neuropsychiatric events, such as hallucinations and night terrors, reported by HIV patients taking it as a medication.

The Inverse Agonist Of CB1 Receptor SR141716A Blocks Compulsive Eating Of Palatable Food. Dore R, Valenza M, Wang X, Rice KC, Sabino V, Cottone P. Addiction Biology, 2013. epub ahead of print.

Dieting and the increased availability of highly palatable food are considered major contributing factors to the large incidence of eating disorders and obesity. This study was aimed at investigating the role of the cannabinoid (CB) system in a novel animal model of compulsive eating, based on a rapid palatable diet cycling protocol. Male Wistar rats were fed either continuously a regular chow diet (Chow/Chow, control group) or intermittently a regular chow diet for 2 days and a palatable, high-sucrose diet for 1 day (Chow/Palatable). Chow/Palatable rats showed spontaneous and progressively increasing hypophagia and body weight loss when fed the regular chow diet, and excessive food intake and body weight gain when fed the palatable diet. Diet cycled rats dramatically escalated the intake of the palatable diet during the first hour of renewed access (7.5 fold compared to controls), and after withdrawal they showed compulsive eating and heightened risk-taking behavior. The inverse agonist of the CB1 receptor, SR141716A reduced the excessive intake of palatable food with higher potency and the body weight with greater efficacy in Chow/Palatable rats, compared to controls. Moreover, SR141716A reduced compulsive eating and risk-taking behavior in Chow/Palatable rats. Finally, consistent with the behavioral and pharmacological observations, withdrawal from the palatable diet decreased the gene expression of the enzyme fatty acid amide hydrolase in the ventromedial hypothalamus while increasing that of CB1 receptors in the dorsal striatum in Chow/Palatable rats, compared to controls. Taken together, these findings are useful in the investigation of the etiology of compulsive eating.

Molecular Neurobiology Branch

Altered Reward Circuitry In the Norepinephrine Transporter Knockout Mouse. Gallagher JJ, Zhang X, Hall FS, Uhl GR, Bearer EL, Jacobs RE. PLoS ONE, March 4, 2013.

Synaptic levels of the monoamine neurotransmitters dopamine, serotonin, and norepinephrine are modulated by their respective plasma membrane transporters, albeit with a few exceptions. Monoamine transporters remove monoamines from the synaptic cleft and thus influence the degree and duration of signaling. Abnormal concentrations of these neuronal transmitters are implicated in a number of neurological and psychiatric disorders, including addiction, depression, and attention deficit/hyperactivity disorder. This work concentrates on the norepinephrine transporter (NET), using a battery of in vivo magnetic resonance imaging techniques and histological correlates to probe the effects of genetic deletion of the norepinephrine transporter on brain metabolism, anatomy and functional connectivity. MRS recorded in the striatum of NET knockout mice indicated a lower concentration of NAA that correlates with histological observations of subtle dysmorphisms in the striatum and internal capsule. As with DAT and SERT knockout mice, the authors detected minimal structural alterations in NET knockout mice by tensor-based morphometric analysis. In contrast, longitudinal imaging after stereotaxic prefrontal cortical injection of manganese, an established neuronal circuitry tracer, revealed that the reward circuit in the NET knockout mouse is biased toward anterior portions of the brain. This is similar to previous results observed for the dopamine transporter (DAT) knockout mouse, but dissimilar from work with serotonin transporter (SERT) knockout mice where Mn(2+) tracings extended to more

posterior structures than in wildtype animals. These observations correlate with behavioral studies indicating that SERT knockout mice display anxiety-like phenotypes, while NET knockouts and to a lesser extent DAT knockout mice display antidepressant-like phenotypic features. Thus, the mainly anterior activity detected with manganese-enhanced MRI in the DAT and NET knockout mice is likely indicative of more robust connectivity in the frontal portion of the reward circuit of the DAT and NET knockout mice compared to the SERT knockout mice.

The Selective M Opioid Receptor Antagonist B-Funaltrexamine Attenuates Methamphetamine-Induced Stereotypical Biting In Mice. Kitanaka J, Kitanaka N, Hall FS, Uhl GR, Fukushima y, Sawai T, Watabe K, Kubo H, Takahashi H, Tanaka K, Nishiyama N, Tatsuta T, Morita Y, Takemura M. Brain Research, July 19, 2013.
The authors investigated whether pretreatment with opioid receptor antagonists affected methamphetamine (METH)-induced stereotypy in mice. Pretreatment of male ICR mice with naloxone, a relatively non-selective opioid receptor antagonist, significantly attenuated the total incidence of METH-induced stereotypical behavior compared with saline vehicle-pretreated subjects. Furthermore, the distribution of METH-induced stereotypical behavior was affected by naloxone administration. Thus, METH-induced stereotypical sniffing and persistent locomotion were significantly increased by naloxone treatment while stereotypical biting was reduced. One way to interpret this pattern of effects is that pretreatment with naloxone appeared to produce a shift in the dose-response curve for METH. Thus, while the more intense forms of oral-facial stereotypies were reduced, increased persistent locomotion was observed in mice given naloxone followed by METH. The selective μ opioid receptor antagonist β-funaltrexamine, but not nor-binaltorphimine (a κ-selective antagonist) nor naltrindole (a δ-selective antagonist), mimicked the effect of naloxone. These observations suggest that opioid receptor antagonists may attenuate METH-induced stereotypical biting in mice via μ opioid receptors, and suggest that antagonism of this system may be a potential therapeutic approach to reducing some deleterious effects of METH use and perhaps in the treatment of some forms of self-injurious behavior.

B(0)AT2 (SLC6A15) Is Localized To Neurons and Astrocytes, and Is Involved In Mediating the Effect Of Leucine In the Brain. Hagglund MG, Roshanbin S, Lofgvist E, Hellsten SV, Nilsson VC, Todkar A, Zhu Y, Stephansson O, Drgonova J, Uhl GR, Schioth HB, Fredriksson R. PLoS ONE, March 7, 2013.
The B(0)AT2 protein is a product of the SLC6A15 gene belonging to the SLC6 subfamily and has been shown to be a transporter of essential branched-chain amino acids. The authors aimed to further characterize the B(0)AT2 transporter in CNS, and to use Slc6a15 knock out (KO) mice to investigate whether B(0)AT2 is important for mediating the anorexigenic effect of leucine. They used the Slc6a15 KO mice to investigate the role of B(0)AT2 in brain in response to leucine and in particular the effect on food intake. Slc6a15 KO mice show lower reduction of food intake as well as lower neuronal activation in the ventromedial hypothalamic nucleus (VMH) in response to leucine injections compared to wild type mice. They also used RT-PCR on rat tissues, in situ hybridization and immunohistochemistry on mouse CNS tissues to document in detail the distribution of SLC6A15 on gene and protein levels. They showed that B(0)AT2 immunoreactivity is mainly neuronal, including localization in many GABAergic neurons and spinal cord motor neurons. B(0)AT2 immunoreactivity was also

found in astrocytes close to ventricles, and co-localized with cytokeratin and diazepam binding inhibitor (DBI) in epithelial cells of the choroid plexus. The data suggest that B(0)AT2 play a role in leucine homeostasis in the brain.

An Evaluation Of the Serotonin System and Perseverative, Compulsive, Stereotypical, and Hyperactive Behaviors In Dopamine Transporter (DAT) Knockout Mice. Fox MA, Panessiti MG, Hall FS, Uhl GR, Murphy DL. Psychopharmacology, June 2013.
Mice lacking the dopamine transporter (DAT) display major behavioral alterations that include hyperactivity, perseverative locomotor patterns, and reduced prepulse inhibition of the acoustic startle reflex. The objectives of this study were to investigate perseverative, compulsive, stereotypical, and hyperactive behaviors, as well as serotonin and its involvement with these behaviors, in DAT gene-altered mice. In the open field, mean turn angle and meandering were decreased in DAT knockout (DAT-KO) mice. DAT-KO mice displayed increased hyperactivity, increased velocity, less time immobile, and a failure to habituate over time in the open field unlike their DAT wildtype (DAT-WT) and heterozygous (DAT-HET) littermates. DAT-KO mice buried fewer marbles than DAT-WT and -HET mice in an assessment of compulsive-like behaviors, likely due to extreme hyperactivity and related inattention. Stereotypical head weaving was increased in untreated DAT-KO mice. Following administration of the 5-HT1A/7 agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), stereotypical head weaving and forepaw treading were increased more in DAT-KO mice than in DAT-WT or -HET mice. By contrast, head twitches induced by treatment with the 5-HT2A/2C agonist (±)-2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) were similar in mice of all three DAT genotypes. 5-HT1A autoreceptor function was intact in DAT-KO mice. Compared to DAT-WT mice, serotonin levels were increased in DAT-HET and -KO mice in frontal cortex and hippocampus, respectively, and serotonin turnover rates were increased ∼30 % in the striatum of DAT-KO mice. These findings extend and confirm prior behavioral and biochemical characterization of DAT-KO mice. Hyperactivity, stereotypy, and perseverative behaviors are increased in these mice, with brain-area specific increases in serotonin levels and serotonin turnover, and marked increases in postsynaptic 5-HT1A receptor-mediated stereotypic responses.

Exclusive Expression Of VMAT2 In Noradrenergic Neurons Increases Viability Of Homozygous VMAT2 Knockout Mice. Ohara A, Kasahara Y, Yamamoto H, Hata H, Kobayashi H, Numachi Y, Miyoshi I, Hall FS, Uhl GR, Ikeda K, Sora I. Biochemical and Biophysical Research Communications, March 15, 2013.
The vesicular monoamine transporter 2 (VMAT2) translocates monoamine neurotransmitters from the neuronal cytoplasm into synaptic vesicles. Since VMAT2-/- mice die within a few days of birth, it is difficult to analyze the detailed VMAT2 functions using these mice. In this study, the authors generated human VMAT2 transgenic mice that expressed VMAT2 in noradrenergic neurons with the aim to rescue the lethality of VMAT2 deletion. The expression of human VMAT2 in noradrenergic neurons extended the life of VMAT2-/- mice for up to three weeks, and these mice showed severe growth deficiency compared with VMAT2+/+ mice. These results may indicate that VMAT2 expressed in noradrenergic neurons has crucial roles in survival during the first several weeks after birth, and VMAT2 functions in other monoaminergic systems could be required for further extended survival. Although VMAT2 rescue in noradrenergic neurons did not eliminate the increased morbidity and lethality

associated with VMAT2 deletion, the extension of the lifespan in VMAT2 transgenic mice will enable behavioral, pharmacological and pathophysiological studies of VMAT2 function.

Impaired Cliff Avoidance Reaction In Dopamine Transporter Knockout Mice.
Yamashita M, Sakakibara Y, Hall FS, Numachi Y, Yoshida S, Kobayashi H, Uchiumi O, Uhl GR, Kasahara Y, Sora I. Psychopharmacology, June 2013, e-pub February 9, 2013.
Impulsivity is a key feature of disorders that include attention-deficit/hyperactivity disorder (ADHD). The cliff avoidance reaction (CAR) assesses maladaptive impulsive rodent behavior. Dopamine transporter knockout (DAT-KO) mice display features of ADHD and are candidates in which to test other impulsive phenotypes. Impulsivity of DAT-KO mice was assessed in the CAR paradigm. For comparison, attentional deficits were also assessed in prepulse inhibition (PPI) in which DAT-KO mice have been shown to exhibit impaired sensorimotor gating. DAT-KO mice exhibited a profound CAR impairment compared to wild-type (WT) mice. As expected, DAT-KO mice showed PPI deficits compared to WT mice. Furthermore, the DAT-KO mice with the most impaired CAR exhibited the most severe PPI deficits. Treatment with methylphenidate or nisoxetine ameliorated CAR impairments in DAT-KO mice. These results suggest that DAT-KO mice exhibit impulsive CAR behavior that correlates with their PPI deficits. Blockade of monoamine transporters, especially the norepinephrine transporter (NET) in the prefrontal cortex (PFC), may contribute to pharmacological improvement of impulsivity in these mice.

Personalized Medicine and Opioid Analgesic Prescribing For Chronic Pain: Opportunities and Challenges. Bruehl S, Apkarian AV, Ballantyne JC, Berger A, Borsook D, Chen WG, Farrar JT, Haythornthwaite JA, Horn SD, Iadarola MJ, Inturrisi CE, Lao L, Mackey S, Mao J, Sawczuk A, Uhl GR, Witter J, Woolf CJ, Zubieta JK, Lin Y. The Journal of Pain 2013; 14(2): 103-113.
Use of opioid analgesics for pain management has increased dramatically over the past decade, with corresponding increases in negative sequelae including overdose and death. There is currently no well-validated objective means of accurately identifying patients likely to experience good analgesia with low side effects and abuse risk prior to initiating opioid therapy. This paper discusses the concept of data-based personalized prescribing of opioid analgesics as a means to achieve this goal. Strengths, weaknesses, and potential synergism of traditional randomized placebo-controlled trial (RCT) and practice-based evidence (PBE) methodologies as means to acquire the clinical data necessary to develop validated personalized analgesic-prescribing algorithms are overviewed. Several predictive factors that might be incorporated into such algorithms are briefly discussed, including genetic factors, differences in brain structure and function, differences in neurotransmitter pathways, and patient phenotypic variables such as negative affect, sex, and pain sensitivity. Currently available research is insufficient to inform development of quantitative analgesic-prescribing algorithms. However, responder subtype analyses made practical by the large numbers of chronic pain patients in proposed collaborative PBE pain registries, in conjunction with follow-up validation RCTs, may eventually permit development of clinically useful analgesic-prescribing algorithms. Since current research is insufficient to base opioid analgesic prescribing on patient characteristics, collaborative PBE studies in large, diverse pain patient samples in conjunction with follow-up RCTs may permit development of quantitative

analgesic-prescribing algorithms that could optimize opioid analgesic effectiveness and mitigate risks of opioid-related abuse and mortality.

Serotonergic Involvement In the Amelioration Of Behavioral Abnormalities In Dopamine Transporter Knockout Mice By Nicotine. Uchiumi O, Kasahara Y, Fukui A, Hall FS, Uhl GR, Sora I. Neuropharmacology, January 2013.

Dopamine transporter knockout (DAT KO) mice exhibit elevated extracellular dopamine levels in brain regions that include the striatum and the nucleus accumbens, but not the prefrontal cortex. DAT KO mice model some aspects of psychiatric disorders, including schizophrenia. Smoking is more common in patients with schizophrenia, suggesting that nicotine might ameliorate aspects of the behavioral abnormalities and/or treatment side effects seen in these individuals. The authors report nicotine-induced normalization of effects on locomotion and prepulse inhibition of acoustic startle (PPI) in DAT KO mice that require intact serotonin 5-HT1A systems. First, they observed that the marked hyperactivity displayed by DAT KO mice was reduced by administration of nicotine. This nicotine effect was blocked by pretreatment with the non-specific nicotinic acetylcholine (nACh) receptor antagonist mecamylamine, or the 5-HT1A antagonist WAY100635. Secondly, the authors examined the effects of nicotine on PPI in DAT KO mice. Treatment with nicotine significantly ameliorated the PPI deficits observed in DAT KO mice. The ameliorating action of nicotine on PPI deficits in DAT KO mice was blocked by mecamylamine, the α_7 nACh receptor antagonist methyllycaconitine or WAY100635, while the $\alpha_4\beta_2$ nACh receptor antagonist dihydro-β-erythroidinehydrobromide (DHβE) produced only a non-significant trend toward attenuation of nicotine effects. Finally, they observed that administration of the 5-HT1A receptor agonist 8-OH-DPAT also ameliorated the deficit in PPI observed in DAT KO mice. This amelioration was antagonized by pretreatment with WAY100635. These data support the idea that nicotine might ameliorate some of the cognitive dysfunctions found in schizophrenia in a 5-HT1A-dependent fashion.

Active Behaviours Produced By Antidepressants and Opioids In the Mouse Tail Suspension Test. Berrocoso E, Ikeda K, Sora I, Uhl GR, Sanchez-Blazquez P, Mico JA. The International Journal of Neuropsychopharmacology, February 2013.

Most classical preclinical tests to predict antidepressant activity were initially developed to detect compounds that influenced noradrenergic and/or serotonergic activity, in accordance with the monoaminergic hypothesis of depression. However, central opioid systems are also known to influence the pathophysiology of depression. While the tail suspension test (TST) is very sensitive to several types of antidepressant, the traditional form of scoring the TST does not distinguish between different modes of action. The present study was designed to compare the behavioural effects of classical noradrenergic and/or serotonergic antidepressants in the TST with those of opioids. The authors developed a sampling technique to differentiate between behaviours in the TST, namely, curling, swinging and immobility. Antidepressants that inhibit noradrenaline and/or serotonin re-uptake (imipramine, venlafaxine, duloxetine, desipramine and citalopram) decreased the immobility of mice, increasing their swinging but with no effect on their curling behaviour. No differences were observed between antidepressants that act on noradrenergic or serotoninergic transmission. While opioid compounds also decreased the immobility of the mice [morphine, codeine, levorphanol, (-)-methadone, (±)-tramadol and (+)-tramadol], they selectively increased curling behaviour.

Blocking opioid receptors with naloxone prevented the antidepressant-like effect of codeine, and μ-opioid receptor knockout decreased normal curling behaviour and blocked (±)-tramadol-induced curling, further demonstrating the reliability and validity of this approach. These results show that at least two behaviourally distinct processes occur in the TST, highlighting the antidepressant-like effects of opioids evident in this test. Furthermore, our data suggest that swinging and curling behaviours are mediated by enhanced monoamine and opioid neurotransmission, respectively.

Biomarkers For Smoking Cessation. Bough KJ, Lerman C, Rose JE, McClernon FJ, Kenny PJ, Tyndale RF, David SP, Stein EA, Uhl GR, Conti DV, Green C, Amur S. Clinical Pharmacology and Therapeutics, June 2013.
One way to enhance therapeutic development is through the identification and development of evaluative tools such as biomarkers. This review focuses on putative diagnostic, pharmacodynamic, and predictive biomarkers for smoking cessation. These types of biomarkers may be used to more accurately diagnose a disease, personalize treatment, identify novel targets for drug discovery, and enhance the efficiency of drug development. Promising biomarkers are presented across a range of approaches including metabolism, genetics, and neuroimaging. A preclinical viewpoint is also offered, as are analytical considerations and a regulatory perspective summarizing a pathway toward biomarker qualification.

Behavioral Neuroscience Branch

Neurobiology of Relapse Section

Effect Of Chronic Delivery Of the Toll-Like Receptor 4 Antagonist (+)-Naltrexone On Incubation Of Heroin Craving. Theberge FR, Li A, Kambhampati S, Pickens, CL, Bossert JM, Baumann MH, Hutchinson MR, Rice RC, Watkins LR, Shaham Y. Biological Psychiatry 2013; 73:729-737.
Recent evidence implicates toll-like receptor 4 (TLR4) in opioid analgesia, tolerance, conditioned place preference, and self-administration. Here, the authors determined the effect of the TLR4 antagonist (+)-naltrexone (a μ-opioid receptor inactive isomer) on the time-dependent increases in cue-induced heroin seeking after withdrawal (incubation of heroin craving). In an initial experiment, they trained rats for 9 hours per day to self-administer heroin (.1 mg/kg/infusion) for 9 days; lever presses were paired with a 5-second tone-light cue. They then assessed cue-induced heroin seeking in 30-minute extinction sessions on withdrawal day 1; immediately after testing, they surgically implanted rats with Alzet minipumps delivering (+)-naltrexone (0, 7.5, 15, 30 mg/kg/day, subcutaneous) for 14 days. They then tested the rats for incubated cue-induced heroin seeking in 3-hour extinction tests on withdrawal day 13. They found that chronic delivery of (+)-naltrexone via minipumps during the withdrawal phase decreased incubated cue-induced heroin seeking. In follow-up experiments, the authors found that acute injections of (+)-naltrexone immediately before withdrawal day 13 extinction tests had no effect on incubated cue-induced heroin seeking. Furthermore, chronic delivery of (+)-naltrexone (15 or 30 mg/kg/day) or acute systemic injections (15 or 30 mg/kg) had no effect on ongoing extended access heroin self-administration. Finally, in rats trained to self-administer methamphetamine (.1 mg/kg/infusion, 9 hours/day, 9 days), chronic delivery of (+)-

naltrexone (30 mg/kg/day) during the withdrawal phase had no effect on incubated cue-induced methamphetamine seeking. The present results suggest a critical role of TLR4 in the development of incubation of heroin, but not methamphetamine, craving.

Critical Role Of Peripheral Actions Of Nicotine in the Development of Neural and Behavioral Sensitization. Lenoir M, Tang JS, Kiyatkin EA. The Journal of Neuroscience 2013; 33: 9937-9949.

Repeated exposure to nicotine and other psychostimulant drugs produces persistent increases in their psychomotor and physiological effects (sensitization), a phenomenon related to the drugs' reinforcing properties and abuse potential. Here, the authors examined the role of peripheral actions of nicotine in nicotine-induced sensitization of centrally mediated physiological parameters (brain, muscle, and skin temperatures), cortical and VTA EEG, neck EMG activity, and locomotion in freely moving rats. Repeated injections of intravenous nicotine (30 μg/kg) induced sensitization of the drug's effects on all these measures. In contrast, repeated injections of the peripherally acting analog of nicotine, nicotine pyrrolidine methiodide (nicotinePM, 30 μg/kg, i.v.) resulted in habituation (tolerance) of the same physiological, neuronal, and behavioral measures. However, after repeated nicotine exposure, acute nicotinePM injections induced nicotine-like physiological responses: powerful cortical and VTA EEG desynchronization, EMG activation, a large brain temperature increase, but weaker hyperlocomotion. Additionally, both the acute locomotor response to nicotine and nicotine-induced locomotor sensitization were attenuated by blockade of peripheral nicotinic receptors by hexamethonium (3 mg/kg, i.v.). These data suggest that the peripheral actions of nicotine, which precede its direct central actions, serve as a conditioned interoceptive cue capable of eliciting nicotine-like physiological and neural responses after repeated nicotine exposure. Thus, by providing a neural signal to the CNS that is repeatedly paired with the direct central effects of nicotine, the drug's peripheral actions play a critical role in the development of nicotine-induced physiological, neural, and behavioral sensitization.

Conditioned Contribution Of Peripheral Cocaine Actions To Cocaine Reward and Cocaine-Seeking. Wang B, You ZB, Oleson EB, Cheer JF, Myal S, Wise RA. Neuropsychopharmacology. 2013 Aug; 38(9): 1763-1769. doi: 10.1038/npp.2013.75. Epub 2013 Mar 27.

Cocaine has actions in the peripheral nervous system that reliably precede—and thus predict—its soon-to-follow central rewarding effects. In cocaine-experienced animals, the peripheral cocaine signal is relayed to the central nervous system, triggering excitatory input to the ventral tegmental origin of the mesocorticolimbic dopamine system, the system that mediates the rewarding effects of the drug. The authors used cocaine methiodide, a cocaine analog that does not cross the blood–brain barrier, to isolate the peripheral actions of cocaine and determine their central and behavioral effects in animals first trained to lever-press for cocaine hydrochloride (the centrally acting and abused form of the drug). They first confirmed with fast-scan cyclic voltammetry that cocaine methiodide causes rapid dopamine release from dopamine terminals in cocaine hydrochloride-trained rats. They then compared the ability of cocaine hydrochloride and cocaine methiodide to establish conditioned place preferences in rats with self-administration experience. While cocaine hydrochloride established stronger place preferences, cocaine methiodide was also effective and its effectiveness increased (incubated) over weeks of cocaine abstinence. Cocaine self-administration was extinguished

when cocaine methiodide or saline was substituted for cocaine hydrochloride in the intravenous self-administration paradigm, but cocaine hydrochloride and cocaine methiodide each reinstated non-rewarded lever-pressing after extinction. Rats extinguished by cocaine methiodide substitution showed weaker cocaine-induced reinstatement than rats extinguished by saline substitution. These findings suggest that the conditioned peripheral effects of cocaine can contribute significantly to cocaine-induced (but not stress-induced) cocaine craving, and also suggest the cocaine cue as an important target for cue-exposure therapies for cocaine addiction.

Neurocircuitry of Motivation Section

Cocaine Drives Aversive Conditioning Via Delayed Activation Of Dopamine-Responsive Habenular and Midbrain Pathways. Jhou TC, Good CH, Rowley CS, Xu SP, Wang H, Burnham NW, Hoffman AF, Lupica CR, Ikemoto S. J Neurosci. 2013 Apr 24; 33(17): 7501-7512. doi: 10.1523/JNEUROSCI.3634-12.2013. PubMed PMID: 23616555.
Many strong rewards, including abused drugs, also produce aversive effects that are poorly understood. For example, cocaine can produce aversive conditioning after its rewarding effects have dissipated, consistent with opponent process theory, but the neural mechanisms involved are not well known. Using electrophysiological recordings in awake rats, the authors found that some neurons in the lateral habenula (LHb), where activation produces aversive conditioning, exhibited biphasic responses to single doses of intravenous cocaine, with an initial inhibition followed by delayed excitation paralleling cocaine's shift from rewarding to aversive. Recordings in LHb slice preparations revealed similar cocaine-induced biphasic responses and further demonstrated that biphasic responses were mimicked by dopamine, that the inhibitory phase depended on dopamine D2-like receptors, and that the delayed excitation persisted after drug washout for prolonged durations consistent with findings in vivo. c-Fos experiments further showed that cocaine-activated LHb neurons preferentially projected to and activated neurons in the rostromedial tegmental nucleus (RMTg), a recently identified target of LHb axons that is activated by negative motivational stimuli and inhibits dopamine neurons. Finally, pharmacological excitation of the RMTg produced conditioned place aversion, whereas cocaine-induced avoidance behaviors in a runway operant paradigm were abolished by lesions of LHb efferents, lesions of the RMTg, or by optogenetic inactivation of the RMTg selectively during the period when LHb neurons are activated by cocaine. Together, these results indicate that LHb/RMTg pathways contribute critically to cocaine-induced avoidance behaviors, while also participating in reciprocally inhibitory interactions with dopamine neurons.

Molecular Mechanisms of Behavior Unit

Unique Gene Alterations Are Induced In FACS-Purified Fos-Positive Neurons Activated During Cue-Induced Relapse To Heroin Seeking. Fanous SA, Guez-Barber DH, Goldart EM, Schrama R, Theberge F, Shaham Y, Hope BT. J. Neurochem. 2013; 124: 100-108.
Cue-induced heroin seeking after prolonged withdrawal is associated with neuronal activation and altered gene expression in prefrontal cortex (PFC). However, these previous studies

assessed gene expression in all neurons regardless of their activity state during heroin seeking. Using Fos as a marker of neural activity, the authors describe distinct molecular alterations induced in activated versus non-activated neurons during cue-induced heroin seeking after prolonged withdrawal. They trained rats to self-administer heroin for 10 days (6-h/day) and assessed cue-induced heroin seeking in extinction tests after 14 or 30 days. The authors used fluorescent-activated cell-sorting (FACS) to purify Fos-positive and Fos-negative neurons from PFC 90 min after extinction testing. Flow cytometry showed that Fos-immunoreactivity was increased in less than 10% of sparsely distributed PFC neurons. mRNA levels of the immediate early genes fosB, arc, egr1, and egr2, as well as npy and map2k6, were increased in Fos-positive, but not Fos-negative, neurons. In support of these findings, double-label immunohistochemistry indicated substantial co-expression of NPY- and Arc-immunoreactivity in Fos-positive neurons. These data indicate that cue-induced relapse to heroin seeking after prolonged withdrawal induces unique molecular alterations within activated PFC neurons that are distinct from those observed in the surrounding majority of non-activated neurons.

Preclinical Pharmacology Section

Peroxisome Proliferator-Activated Receptor (PPAR) Agonists As Promising New Medications For Drug Addiction: Preclinical Evidence. Le Foll B, Di Ciano P, Panlilio LV, Goldberg SR, Ciccocioppo R. Current Drug Targets, 2013; 14: 768-776.
This review examines the growing literature on the role of peroxisome proliferator-activated receptors (PPARs) in addiction. There are two subtypes of PPAR receptors that have been studied in addiction: PPAR-α and PPAR-γ. The role of each PPAR subtype in common models of addictive behavior, mainly pre-clinical models, is summarized. In particular, studies are reviewed that investigated the effects of PPAR-α agonists on relapse, sensitization, conditioned place preference, withdrawal and drug intake, and effects of PPAR-γ agonists on relapse, withdrawal and drug intake. Finally, studies that investigated the effects of PPAR agonists on neural pathways of addiction are reviewed. Taken together these preclinical data indicate that PPAR agonists are promising new medications for drug addiction treatment.

CREB Phosphorylation Regulates Striatal Transcriptional Responses In the Self-Administration Model Of Methamphetamine Addiction In The Rat. Krasnova IN, Chiflikyan M, Justinova Z, McCoy MT, Ladenheim B, Jayanthi S, Quintero C, Brannock C, Barnes C, Adair JE, Lehrmann E, Kobeissy FH, Gold MS, Becker KG, Goldberg SR, Cadet JL. Neurobiology of Disease 2013, epub May 29, 2013.
Neuroplastic changes in the dorsal striatum participate in the transition from casual to habitual drug use and might play a critical role in the development of methamphetamine (METH) addiction. The authors examined the influence of METH self-administration on gene and protein expression that may form substrates for METH-induced neuronal plasticity in the dorsal striatum. Male Sprague-Dawley rats self-administered METH (0.1mg/kg/injection, i.v.) or received yoked saline infusions during eight 15-h sessions and were euthanized 2h, 24h, or 1month after cessation of METH exposure. Changes in gene and protein expression were assessed using microarray analysis, RT-PCR and Western blots. Chromatin immunoprecipitation (ChIP) followed by PCR was used to examine epigenetic regulation of METH-induced transcription. METH self-administration caused increases in mRNA

expression of the transcription factors, c-fos and fosb, the neurotrophic factor, Bdnf, and the synaptic protein, synaptophysin (Syp) in the dorsal striatum. METH also caused changes in ΔFosB, BDNF and TrkB protein levels, with increases after 2 and 24h, but decreases after 1month of drug abstinence. Importantly, ChIP-PCR showed that METH self-administration caused enrichment of phosphorylated CREB (pCREB), but not of histone H3 trimethylated at lysine 4 (H3K4me3), on promoters of c-fos, fosb, Bdnf and Syp at 2h after cessation of drug intake. These findings show that METH-induced changes in gene expression are mediated, in part, by pCREB-dependent epigenetic phenomena. Thus, METH self-administration might trigger epigenetic changes that mediate alterations in expression of genes and proteins serving as substrates for addiction-related synaptic plasticity.

The Effects Of Anandamide Signaling Enhanced By the FAAH Inhibitor URB597 On Coping Styles In Rats. Haller J, Goldberg SR, Pelczer KG, Aliczki M, Panlilio LV. Psychopharmacology (Berl). 2013, epub June 7, 2013.
Coping styles are fundamental characteristics of behavior that affect susceptibility to, and resilience during, mental and physical illness. Shifts from passive to active coping are considered therapeutic goals in many stress-related disorders, but the neural control of coping is poorly understood. Based on earlier findings, the authors hypothesized that coping styles are influenced by endocannabinoids. Here, they tested whether FAAH inhibition by URB597 affects behaviors aimed at controlling a critical situation and the degree to which environmental stimuli influence behavior i.e., we studied the impact of URB597 on the two main attributes of coping styles. Rats were tested in the tail-pinch test of coping and in the elevated plus-maze test that was performed under highly divergent conditions. Under the effects of URB597, rats focused their behavior more on the discomfort-inducing clamp in the tail-pinch test, i.e., they coped with the challenge more actively. In the elevated plus-maze, URB597-treated rats demonstrated an autonomous behavioral control by reducing both "wariness" induced by aversive conditions and "carelessness" resulting from favorable conditions. URB597 treatment-induced behavioral changes indicated a shift towards active coping with challenges. This behavioral change appears compatible with the previously suggested role of endocannabinoids in emotional homeostasis. Albeit further studies are required to characterize the role of endocannabinoids in coping, these findings suggest that the enhancement of endocannabinoid signaling may become a therapeutic option in emotional disorders characterized by passive coping (e.g., anxiety and depression) and in physical diseases where active coping is therapeutically desirable.

Neuroimaging Research Branch

Dorsolateral Caudate Nucleus Differentiates Cocaine From Natural Reward Associated Contextual Cues. Liu H-S, Chefer S, Lu H, Guillen K, Rea W, Kurup P, Yang Y, Peoples LL, Stein EA. Proc. Nat'l Acad Sci (USA) 2013; 110: 4093-4098.
Chronic drug administration induces neuroplastic changes within brain circuits regulating cognitive control and/or emotions. Following repeated pairings between drug intake and environmental cues, increased sensitivity to or salience of these contextual cues provoke conscious or unconscious craving and enhance susceptibility to relapse. To explore brain circuits participating in such experience-induced plasticity, the authors combined functional

MRI with a preclinical drug vs. food self-administration (SA) withdrawal model. Specifically, two groups of rats were trained to associate odor cues with the availability of i.v. cocaine or oral sucrose, respectively. After 20 d of cocaine or sucrose SA followed by prolonged (30 d) forced abstinence, animals were presented with odor cues previously associated with or without (S+/S-) reinforcer (cocaine/sucrose) availability while undergoing functional MRI scans. ANOVA results demonstrate that a learning effect distinguishing S+ from S- was seen in the insula and nucleus accumbens, with the insula response reflecting the individual history of cocaine SA intake. A main effect of group, distinguishing cocaine from sucrose, was seen in the medial prefrontal cortex (infralimbic, prelimbic, and cingulate cortex) and dorsolateral striatum. Critically, only the dorsomedial striatum demonstrated a double dissociation between the two SA groups and learning (S+ vs. S-). These findings demonstrate altered cortico-limbic-striatal reward-related processing to learned, environment reward-associated contextual odor cues, which may serve as potential biomarkers for therapeutic interventions.

Insula's Functional Connectivity With Ventromedial Prefrontal Cortex Mediates the Impact Of Trait Alexithymia On State Tobacco Craving. Sutherland MT, Carroll AJ, Salmeron BJ, Ross TJ, Stein EA. Psychopharmacology 2013; 228: 143-155.
Alexithymia is a personality trait characterized by difficulty indentifying and describing subjective emotional experiences. Decreased aptitude in the perception, evaluation, and communication of affectively laden mental states has been associated with reduced emotion regulation, more severe drug craving in addicts, and structural/functional alterations in insula and anterior cingulate cortex (ACC). The insula and ACC represent sites of convergence between the putative neural substrates of alexithymia and those perpetuating cigarette smoking. The authors examined the interrelations between alexithymia, tobacco craving, and insula/ACC neurocircuitry using resting-state functional connectivity (rsFC). Overnight-deprived smokers (n = 24) and nonsmokers (n = 20) completed six neuroimaging assessments on different days both in the absence of, and following, varenicline and/or nicotine administration. In this secondary analysis of data from a larger study, the authors assessed trait alexithymia and state tobacco craving using self-reports and examined the rsFC of bilateral insular subregions (anterior, middle, posterior) and dorsal ACC. Higher alexithymia in smokers predicted reduced rsFC strength between the right anterior insula (aI) and ventromedial prefrontal cortex (vmPFC). Higher alexithymia also predicted more severe tobacco craving during nicotine withdrawal. Critically, the identified aI-vmPFC circuit fully mediated this alexithymia-craving relation. That is, elevated alexithymia predicted decreased aI-vmPFC rsFC and, in turn, decreased aI-vmPFC rsFC predicted increased craving during withdrawal. A moderated mediation analysis indicated that this aI-vmPFC mediational effect was not observed following drug administration. These results suggest that a weakened right aI-vmPFC functional circuit confers increased liability for tobacco craving during smoking abstinence. Individual differences in alexithymia and/or aI-vmPFC functional coupling may be relevant factors for smoking cessation.

Down-Regulation Of Amygdala and Insula Functional Circuits By Varenicline and Nicotine In Abstinent Cigarette Smokers. Sutherland MT, Carroll AJ, Salmeron BJ, Ross TJ, Hong E, Stein, EA. Biological Psychiatry 2013 Mar 15. doi:pii: S0006-3223(13)00137-6. 10.1016/j.biopsych.2013.01.035. [Epub ahead of print] PMID: 23506999.

Although the amygdala and insula are regarded as critical neural substrates perpetuating cigarette smoking, little is known about their circuit-level interactions with interconnected regions during nicotine withdrawal or following pharmacotherapy administration. To elucidate neurocircuitry associated with early smoking abstinence, the authors examined the impact of varenicline and nicotine, two modestly efficacious pharmacologic cessation aids, on amygdala- and insula-centered circuits using resting-state functional connectivity (rsFC). In a functional magnetic resonance imaging study employing a two-drug, placebo-controlled design, 24 overnight-abstinent smokers and 20 nonsmokers underwent ~17 days of varenicline and placebo pill administration and were scanned, on different days under each condition, wearing a transdermal nicotine or placebo patch. The authors examined the impact of varenicline and nicotine (both alone and in combination) on amygdala- and insula-centered rsFC using seed-based assessments. Beginning with a functionally defined amygdala seed, they observed that rsFC strength in an amygdala-insula circuit was down-regulated by varenicline and nicotine in abstinent smokers. Using this identified insula region as a new seed, both drugs similarly decreased rsFC between the insula and constituents of the canonical default-mode network (posterior cingulate cortex, ventromedial/dorsomedial prefrontal cortex, parahippocampus). Drug-induced rsFC modulations were critically linked with nicotine withdrawal, as similar effects were not detected in nonsmokers. These results suggest that nicotine withdrawal is associated with elevated amygdala-insula and insula-default-mode network interactions. As these potentiated interactions were down-regulated by two pharmacotherapies, this effect may be a characteristic shared by pharmacologic agents promoting smoking cessation. Decreased rsFC in these circuits may contribute to amelioration of subjective withdrawal symptoms.

The Roles Of Reward, Default, and Executive Control Networks In Set-Shifting Impairments in Schizophrenia. Waltz JA, Kasanova, Z, Ross TJ, Salmeron BJ, McMahon, RP, Gold JM, Stein EA. PLoS ONE 8(2): e57257. doi:10.1371/journal.pone.0057257, 2013. Patients with schizophrenia (SZ) show deficits on tasks of rapid reinforcement learning, like probabilistic reversal learning (PRL), but the neural bases for those impairments are not known. Recent evidence of relatively intact sensitivity to negative outcomes in the ventral striatum (VS) in many SZ patients suggests that PRL deficits may be largely attributable to processes downstream from feedback processing, involving both the activation of executive control task regions and deactivation of default mode network (DMN) components. The authors analyzed data from 29 chronic SZ patients and 21 matched normal controls (NCs) performing a PRL task in an MRI scanner. Subjects were presented with eight pairs of fractal stimuli, for 50 trials each. For each pair, subjects learned to choose the more frequently-rewarded (better) stimulus. Each time a criterion was reached, the better stimulus became the worse one, and the worse became the better. Responses to feedback events were assessed through whole-brain and regions-of-interest (ROI) analyses in DMN. The authors also assessed correlations between BOLD signal contrasts and clinical measures in SZs. Relative to NCs, SZ patients showed comparable deactivation of VS in response to negative feedback, but reduced deactivation of DMN components including medial prefrontal cortex (mPFC). The magnitudes of patients' punishment-evoked deactivations in VS and ventromedial PFC correlated significantly with clinical ratings for avolition/anhedonia. These findings suggest that schizophrenia is associated with a reduced ability to deactivate components of default mode networks, following the presentation of informative feedback and that motivational deficits in SZ relate closely to feedback-evoked activity in reward circuit components. These

results also confirm a role for ventrolateral and dorsomedial PFC in the execution of response-set shifts.

Disruption Of Anterior Insula Modulation Of Large-Scale Brain Networks In Schizophrenia. Moran LV, Tagamets M, Sampath H, Stein EA, Kochunov P, Hong LE. Biological Psych 2013 Apr 24. doi:pii: S0006-3223(13)00261-8. 10.1016/j.biopsych.2013.02.029. [Epub ahead of print] PMID: 23623456.
Systems level modeling of functional magnetic resonance imaging data has demonstrated dysfunction of several large-scale brain networks in schizophrenia. Anomalies across multiple functional networks associated with schizophrenia could be due to diffuse pathology across multiple networks or, alternatively, dysfunction at converging control(s) common to these networks. The right anterior insula has been shown to modulate activity in the central executive and default mode networks in healthy individuals. The authors tested the hypothesis that right anterior insula modulation of central executive and default mode networks is disrupted in schizophrenia and associated with cognitive deficits. In 44 patients with schizophrenia and 44 healthy control subjects, the authors used seed-based resting state functional connectivity functional magnetic resonance imaging analysis to examine connectivity between right insular subregions and central executive/default mode network regions. They also performed two directed connectivity analyses of resting state data: Granger analysis and confirmatory structural equation modeling. Between-group differences in path coefficients were used to evaluate anterior insula modulation of central executive and default mode networks. Cognitive performance was assessed with the rapid visual information processing task, a test of sustained attention. With multiple connectivity techniques, The authors found compelling, corroborative evidence of disruption of right anterior insula modulation of central executive and default mode networks in patients with schizophrenia. The strength of right anterior insula modulation of these networks predicted cognitive performance. Individuals with schizophrenia have impaired right anterior insula modulation of large-scale brain networks. The right anterior insula might be an emergent pathophysiological gateway in schizophrenia.

A Preliminary Study Suggests That Nicotine and Prefrontal Dopamine Affect Cortico-Striatal Areas In Smokers With Performance Feedback. Lee MR, Gallen CL, Ross TR, Kurup P, Salmeron BJ, Hodgkinson CA, Goldman D, Stein EA, Enoch M-A. Genes Brain Behavior 2013Jul; 12(5): 554-563. doi: 10.1111/gbb.12027. Epub 2013 Apr 11. PMID: 23433232.
Nicotine and tonic dopamine (DA) levels [as inferred by catechol-O-methyl tranferase (COMT) Val158Met genotype] interact to affect prefrontal processing. Prefrontal cortical areas are involved in response to performance feedback, which is impaired in smokers. The authors investigated whether there is a nicotine × COMT genotype interaction in brain circuitry during performance feedback of a reward task. They scanned 23 healthy smokers (10 Val/Val homozygotes, 13 Met allele carriers) during two fMRI sessions while subjects were wearing a nicotine or placebo patch. A significant nicotine × COMT genotype interaction for BOLD signal during performance feedback in cortico-striatal areas was seen. Activation in these areas during the nicotine patch condition was greater in Val/Val homozygotes and reduced in Met allele carriers. During negative performance feedback, the change in activation in error detection areas such as anterior cingulate cortex (ACC)/superior frontal gyrus on nicotine

compared to placebo was greater in Val/Val homozygotes compared to Met allele carriers. With transdermal nicotine administration, Val/Val homozygotes showed greater activation with performance feedback in the dorsal striatum, area associated with habitual responding. In response to negative feedback, Val/Val homozygotes had greater activation in error detection areas, including the ACC, suggesting increased sensitivity to loss with nicotine exposure. Although these results are preliminary due to small sample size, they suggest a possible neurobiological mechanism underlying the clinical observation that Val/Val homozygotes, presumably with elevated COMT activity compared to Met allele carriers and therefore reduced prefrontal DA levels, have poorer outcomes with nicotine replacement therapy.

Dual Role Of Nicotine In Addiction and Cognition: A Review Of Neuroimaging Studies In Humans. Jasinska AJ, Zorick T, Brody AL, Stein EA. Neuropharmacology. 2013 Mar 6. doi:pii: S0028-3908(13)00072-5. 10.1016/j.neuropharm.2013.02.015. [Epub ahead of print] PMID: 23474015.

Substantial evidence demonstrates both nicotine's addiction liability and its cognition-enhancing effects. However, the neurobiological mechanisms underlying nicotine's impact on brain function and behavior remain incompletely understood. Elucidation of these mechanisms is of high clinical importance and may lead to improved therapeutics for smoking cessation as well as for a number of cognitive disorders such as schizophrenia. Neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), which make it possible to study the actions of nicotine in the human brain in vivo, play an increasingly important role in identifying these dual mechanisms of action. In this review, the authors summarize the current state of knowledge and discuss outstanding questions and future directions in human neuroimaging research on nicotine and tobacco. This research spans from receptor-level PET and SPECT studies demonstrating nicotine occupancy at nicotinic acetylcholine receptors (nAChRs) and upregulation of nAChRs induced by chronic smoking; through nicotine's interactions with the mesocorticolimbic dopamine system believed to mediate nicotine's reinforcing effects leading to dependence; to functional activity and connectivity fMRI studies documenting nicotine's complex behavioral and cognitive effects manifest by its actions on large-scale brain networks engaged both during task performance and at rest.

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Application Receipt, Referral, and Review

During the October 2013 Council Cycle, NIDA received 1366 applications (872 with NIDA as primary IC assignment). The Office of Extramural Affairs (OEA) managed the programmatic referral process for these applications.

OEA arranged and managed eight Special Emphasis Panel (SEP) grant application review meetings in which applications were peer reviewed for scientific and technical merit and budget recommendations. In addition, OEA staff arranged and managed 19 contract review meetings to evaluate contract proposals and concepts, and the Loan Repayment Review.

Special Emphasis Panel Grant Reviews

Conference Grant Review (R13)
I/START Small Grant Review (R03)
Grand Opportunity in Medications Development for Substance-Related Disorders (U01)
Cohort Studies of HIV/AIDS and Substance Use (U01)

Contract Reviews

SBIR Phase I Concepts:

N43DA-13-5577 – "Technological Tools to Facilitate Implementation of Evidence-Based Substance Abuse Prevention Interventions Among the Military"

N43DA-14-5679 – "ACA Web Platform to Integrate Behavioral Health & Prevention with Primary Care"

N43DA-14-1208 - "Bundled Service for Designing Methodologically Rigorous Animal Studies"

N43DA-14-2239 – "Products to Prevent (Lethal) Drug-Induced Resporatory Depression"

N43DA-14-5578 – "Web Resource System for Prescription Drug Providers, Researchers and Users: The Prescription Drug Abuse Policy System (PDAPS)"

SBIR Phase II Contract Reviews:

N44DA-13-2227 – "Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse "

N44DA-13-2231 – "MEDICAM: Medication Ingestion Compliance and Adherence Monitoring System"

N44DA-13-2232 – "The ID-Cap System for Confirming Compliance"

N44DA-13-4415 – "Improving Treatment Outcomes for Addicted Populations via Take Control – A Kinect VR Game for Windows"

N44DA-13-4416 – "PERSEVERE: Personalized Self-Efficacy Virtual Environment Recovery Experience"

N44DA-13-5569 – "Drugged Driving: Future Research Directions"

N44DA-13-5571 – "National Drugged Driving Reporting System"

N44DA-13-5573 – "The Drugged Driving Information Service"

N44DA-13-5574– "Drug Driving Web-based System"

N44DA-13-2228 – "Feedback-regulated Naloxone Delivery Device to Prevent Opiate Overdose Deaths"

Contract Reviews (R&D and non-R&D)
N01DA-13-8909 – "Profile Screening and Predictive Toxicology"

N01DA-13-8910 – "Analytical Services Center for Medications Development System"

Loan Repayment Review

Certificates of Confidentiality
NIH issues a Certificate of Confidentiality to protect identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information which, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants, and NIH encourages their appropriate use. NIDA OEA issues Certificates of Confidentiality to NIH funded investigators and to non-federally funded investigators for drug abuse and other studies relevant to the NIDA mission. OEA processed 42 Certificate of Confidentiality applications in this Council period.

Privacy Officer Coordination Activities
The Privacy Act provides safeguards for information about individuals maintained in a system of records (i.e. retrievable by name or other identifying information). Records of grant applications, awards, and administration are subject to provisions of the Privacy Act. NIDA OEA houses the Privacy Officer, who evaluates incidents that implicates the Privacy Act, HIPAA, or other Federal regulations which could adversely affect NIH staff or members of the public, expose them to harm, or undermine the public's trust in our ability to safeguard personal information. OEA reviews SBIR or station support contracts to determine if human subjects are involved, and if so, if personally identifiable information was collected and

maintained in a government system of records. In addition, OEA completes Privacy Impact Assessment for new NIDA outward-facing websites.
The Privacy Act requires NIDA to publish, in the Federal Register, notice of NIDA systems of records, whereby we keep information about individuals which can be retrieved by name or other specific identifier. NIDA OEA updates systems of records, determines those no longer relevant to be archived, those to be subsumed into the NIH umbrella system of records, and those needing revision of current data (e.g. location of records, responsible program).

NIDA and NIH introduced a Data Loss Prevention product to assess risks to personally identifiable information (PII) in NIDA, notably social security numbers, which has resulted in a number of Incident Reports to be addressed.

Meetings/Conferences/Service

OEA serves as the NIDA coordinator and liaison for the NIH Guide Publication System, including the Early Notification System. We coordinated the development and publication of 13 NIDA FOAs, including four PARs and nine RFAs:
PAR-13-270 – 7/11/13
PAR-13-259 – 7/3/13
PAR-13-222 – 5/6/13
PAR-13-182 – 4/5/13

DA-14-009 – 6/10/13
DA-14-010 – 6/10/13
DA-14-011 – 6/10/13
DA-14-012 – 6/10/13
DA-14-007 – 5/31/13
DA-14-008 – 5/3/13
DA-14-005 – 5/3/13
DA-14-006 – 5/31/13
DA-14-004 – 4/26/13

CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

- April 30, 2013, to review protocol CTN 0055, Comparing Treatments for HIV-Positive Opioid Users in an Integrated Care Effectiveness Study (CHOICES).
- June 26 and July 11, 2013, to review protocol CTN 0056-Ot, Testing and Linkage to HIV Care in China: a Cluster Randomized Trial.

CONGRESSIONAL AFFAIRS SECTION
(Prepared August 20, 2013)

APPROPRIATIONS

Earlier this year, the President released his FY 2014 Budget. The sequester is not taken into account for purposes of this budget. For NIH, the FY 2014 request is $31.3 billion, an increase of $471 million, or 1.5 percent, over the enacted FY 2012 level. For NIDA, the FY 2014 request is $1.072 billion, an increase of $20.2 million, or approximately 2 percent over the enacted FY 2012 level.

On July 11, 2013, the Senate Appropriations Committee reported out S. 1284, the FY2014 Labor, HHS, Education Appropriations bill making appropriations for the Departments of Labor, Health and Human Services, and Education, and related agencies for the fiscal year ending September 30, 2014. The bill includes $30,954,976,000 for NIH, and $1.064 billion for NIDA.

CONGRESSIONAL MEETINGS/BRIEFINGS

Friends of NIDA Congressional Briefing

On July 10, 2013, the Friends of the National Institute on Drug Abuse coalition hosted a congressional briefing titled "Preventing Prescription Drug Abuse: Applying Science to Solve a Community Epidemic," organized by the government relations office of the American Psychological Association's Science Directorate. This briefing was the 19th in the Friends of NIDA coalition's Charles R. Schuster Educational Briefing Series on Capitol Hill, designed to educate policy makers about current initiatives and advancements in science funded by NIDA. Cosponsored by the Congressional Addiction, Treatment and Recovery Caucus, the Congressional Caucus on Prescription Drug Abuse, and 23 member organizations of the Friends of NIDA, the briefing was attended by over 110 congressional staff, federal agency staff and members of the science advocacy community.

NIDA Director Nora Volkow provided an overview of the Institute's research portfolio on prescription drug abuse and prevention and of current knowledge in the field. Lisa Marsch, psychologist and Director of the Center for Technology and Behavioral Health at the Geisel School of Medicine at Dartmouth, presented NIDA-funded research on technology-based tools for prevention of prescription drug abuse. Amy Haskins, public health educator and sanitarian for the Jackson County Health Department in West Virginia, and project director for the Jackson County Anti-Drug Coalition, presented the story of a community's response to prescription drug abuse. The information in this briefing was presented in the context of a personal story from Phil Bauer, a national advocate for prescription drug safety. Bauer, from York, Pennsylvania, opened the event by sharing the story of the life and death of his son Mark whom he lost to a prescription drug overdose. Mark was a popular high school student who played basketball, led an active social life and was close with his family. His overdose surprised even those who knew him well. Bauer's talk captivated the audience and underscored the need for resources for research and prevention.

SOME BILLS OF INTEREST

HR 486 – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

HR 498 – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. Representatives Rosa DeLauro (D-CT), and Frank Wolf (R-VA) were the only two original co-sponsors of the legislation. The bill was referred to the House Committee on Energy and Commerce.

HR 499 – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

HR 672 -- On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

HR 1263 – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

HR 1285 – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also S 621.

HR 1366 – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

HR 1523 – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

S 237 – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S 264 – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

S 265 – On February 7, 2013, Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

S. 348 – On February 14, 2013, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

S. 621 – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285.

S. 644 – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S. 1277 – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

INTERNATIONAL ACTIVITIES

Binational Agreements

NIDA, Inserm Agree To Cooperate on Research, Training, and Exchange

NIDA and the Institut National de la Santé et de la Recherche Médicale (Inserm) signed an agreement May 7, 2013, to cooperate on neuroscience and psychiatry research to improve understanding and treatment of addiction. Activities under the new agreement will include joint scientific seminars, research development exchange visits, and postdoctoral fellowships. A binational steering committee will identify research areas, such as animal research on the mechanisms of addiction; data sharing and innovative approaches for analyzing imaging, genetic/epigenetic, and clinical datasets; drug discovery for addiction pharmacotherapies; clinical research on addiction with a special emphasis on Phase I and II trials; and biomarkers of addiction including study of the "addictome" and brain imaging. NIDA Director Nora D. Volkow, M.D., hosted the signing ceremony, which was organized by IP Director Steven W. Gust, Ph.D. In his opening remarks, His Excellency François Delattre, Ambassador of France, noted that Dr. Volkow had been awarded the Inserm International Prize for her pioneering work in brain imaging and addiction science, an indication of the commitment NIDA and Inserm share to address the health consequences of addiction. In his plenary address, André Syrota, M.D., chair and chief executive officer of Inserm and president of Alliance Nationale pour les Sciences de la Vie et de la Santé (Aviesan), outlined opportunities for NIDA and Inserm to cooperate in using science to solve the problems of addiction. The binational agreement grew out of a joint meeting held October 15, 2012, where representatives of NIDA, Inserm, and the French Multi-Organization Thematic Institute explored opportunities to enhance collaborative research and research training activities between the United States and France. The agreement with Inserm is the eighth binational agreement NIDA has signed to address mutual research criteria and priorities, develop new international scientific relationships, and significantly enhance existing relationships.

Research Results

Fogarty, NIDA-Funded Research "Making a Difference" in Bulgaria

In research funded by NIDA and the Fogarty International Center (FIC), Jasmin Vassileva, Ph.D., University of Chicago, is investigating the impact of heroin on neurocognitive function and HIV transmission in Bulgaria. Why Bulgaria? In Chicago, up to 80% of heroin users also use cocaine, making it difficult to isolate the effects of a single drug. In contrast, Bulgarian heroin users are more likely to use only that drug. In addition, both heroin addiction and HIV are major public health problems and research is scarce in the country where Dr. Vassileva was born. Dr. Vassileva's project is featured in the FIC series *Making a Difference*, which highlights exemplary global health research projects. Read the full article at http://www.fic.nih.gov/News/Examples/Pages/heroin-bulgaria.aspx.

Fellowships

NIDA Selects Three New Distinguished International Scientists

NIDA has selected senior researchers from Brazil, China, and Taiwan to receive Distinguished International Scientist Collaboration Awards (DISCA). The awards will support a 1-month

research exchange visit between the scientists and their U.S. partners. The DISCA awardees are:

- Felix Kessler, M.D., M.Sc., Ph.D., deputy director of the Center for Drug and Alcohol Research at the Federal University of Rio Grande do Sul, Brazil, will work with George E. Woody, M.D., University of Pennsylvania, to identify treatment interventions that can be adapted and used in research and training programs at the newly funded Brazilian research center. Dr. Kessler will review pharmacotherapy, psychotherapy, counseling, and exercise interventions; genetics and imaging research; and procedures for data management, quality assurance, research publication, and grant writing.
- Former NIDA INVEST Fellow Jiang Du, M.D., Director of the Shanghai Mental Health Center in China, will work with Yih-Ing Hser, Ph.D., University of California, Los Angeles (UCLA). They will adapt interventions for amphetamine-type stimulant use for China, such as those developed by UCLA using contingency management, exercise, mindfulness, and self-management via cell phone. The two also will develop plans for a pilot study to be conducted in Shanghai.
- Tony Szu-Hsien Lee, Ph.D., National Taiwan Normal University, and his DISCA partner, Marek Chawarski, Ph.D., Yale University, will collaboratively develop behavioral and psychosocial interventions to reduce stimulant abuse and promote safer sexual practices among stimulant abusers. Dr. Lee will conduct literature reviews, analyze data, prepare manuscripts for publication, and plan future collaborative research.

CTN INVEST Fellows

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) have jointly offered fellowships to non-U.S. scientists. Each INVEST fellow works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention.

NIDA-International AIDS Society Award Four New Fellowships

NIDA and the International AIDS Society (IAS) have awarded postdoctoral fellowships to scientists from Malaysia, Uganda, and Vietnam. IAS and NIDA cosponsor the fellowships, which provide 18 months of training with an expert in drug abuse-related HIV to advance scientific understanding of the linkages between drug use and HIV while fostering multinational research. The 2013 fellows are:

- Sin How Lim, Ph.D., University of Malaya, Malaysia, will use mobile phones and interactive voice response and intervention technology to collect behavioral data on concurrent substance use and sexual risk behaviors among men who have sex with men in Malaysia. His mentor is Frederick Altice, M.D., M.A., Yale University.
- Francis Bajunirwe, Ph.D., Mbarara University, Uganda, will analyze the impact of alcohol and other substance use on response to antiretroviral treatment in rural Uganda. His mentor is David Bangsberg, M.D., M.P.H., Harvard Medical School.
- Anh Dam Tran, Ph.D., Vietnam, will combine a dynamic epidemic model with a cross-sectional survey to investigate the impact of expanding eligibility criteria for methadone maintenance treatment on drug use, health-related quality of life, and HIV transmission among

Vietnamese drug users. Greg Zaric, University of Western Ontario, Canada, will mentor Dr. Tran, who earned her doctoral degree at the University of New South Wales, Australia, in July 2013.

- Dr. Bach Xuan Tran, Ph.D., Hanoi Medical University, Vietnam, will examine the cost-effectiveness and patients' willingness-to-pay for three models of dispensing methadone to treat opioid dependence in Vietnam. His mentor is Carl Latkin, Ph.D., John Hopkins University.

International Visitors

Seven students and their professor from the Sook-Myung Women's College School of Pharmacological Sciences in South Korea visited NIDA on July 2, 2013. The purpose of the visit was to learn more about the overall mission of NIDA, prevention or intervention programs for drug abuse and what are the roles of pharmacologists in promoting health of public, especially against drug abuse? NIDA staff members Aria Crump, Ph.D., Eve Reider, Ph.D., Augie Diana, Ph.D., Harold Perl, Ph.D. (DESPR), David White, Ph.D. (DPMCDA), Michele Straus, R.Ph., (CCTN) and Dale Weiss (International Program) met with the group.

Other International Activities

Dr. Bruce Hope, IRP, gave an invited lecture the Medical University of Austria in Innsbruck.

Dr. Amy Newman, IRP, was an invited chair and plenary lecturer at the 31st Camerino-Cyprus-Noordwijkerhout Symposium in Camerino, Italy.

Dr. Amy Newman chaired a session and gave an invited lecture at the Dopamine 2013 meeting in Alghero, Italy, in May 2013.

Dr. Oluyomi Okunola-Bakare, IRP, gave an invited lecture at the 31st Camerino-Cyprus-Noordwijkerhout Symposium in Camerino, Italy in May 2013.

Dr. Gianluigi Tanda, IRP, chaired a session and gave an invited lecture at the "Dopamine 2013" conference in Alghero, Italy, May 24-28, 2013.

Dr. Amina Woods presented her paper "The role of protein disorder in functional proteomics" at the Taiwan Proteomics Society International Conference: Recent Advances in Translational Medicine in Taipei, Taiwan, May 24-25, 2013.

Dr. David Gorelick, IRP, organized a symposium on "Etiology and treatment of cannabis dependence" at the 11th World Congress of Biological Psychiatry in Kyoto, Japan in June. At the same Congress, he also organized a symposium on "Advances in transcranial magnetic stimulation (TMS) as treatment for psychiatric disorders."

In June 2013, Ms. Rebecca Hartman, IRP, gave an invited lecture on cannabis effects on driving at the Centre of Forensic Sciences 2nd annual Drugs and Driving Symposium in Toronto, Canada.

Dr. Marilyn Huestis, IRP, was an invited keynote speaker at The International Association of Forensic Toxicologists (TIAFT) 50th Anniversary in London, England. TIAFT is the premier scientific forensic toxicology organization. All living TIAFT past presidents attended; Dr. Huestis is the only female president of the organization over the 50 years. Her keynote lecture was entitled "Chronic Daily Cannabis Smoking: Neuroadaptation, Residual Cannabinoid Excretion & Psychomotor Impairment."

Dr. Marilyn Huestis was an invited speaker at the Italian School on Addiction in Rome, Italy on May 30-31, 2013. The title of her lecture was "The new face of drug abuse: designer synthetic cannabinoids. She also was a panel member discussing future research directions for the joint Italy-NIDA collaboration. She also worked with her Italian colleagues on a joint initiative to characterize the pharmacodynamics and pharmacokinetics of synthetic cannabinoids in vitro, and in vivo in mice and humans.

Dr. Marilyn Huestis was the plenary speaker at the Annual Meeting of the Swiss Society of Legal Medicine. Dr. Huestis spoke on "Designer Synthetic Cannabinoids: the New Face of Drug Abuse.

Dr. Marilyn Huestis toured the World Anti-doping Agency's Lausanne Laboratory, meeting with Dr. Martial Saugy, and toured the Institute of Legal Medicine in Lausanne and met with Dr. Marc Augsberger on new collaborations.

Dr. Marilyn Huestis was invited to give a keynote lecture at the 24th International Symposium on Pharmaceutical and Biomedical Analysis (PBA) in Bologna, Italy. The keynote was entitled "Oral fluid cannabinoids: how analyte and cutoff selection impact drug interpretation."

Dr. Antonello Bonci, IRP, was co-chair of two symposia at the Dopamine 2013 meeting in Sardinia, where he also gave a lecture.

Dr. Yavin Shaham, IRP, gave invited lectures at Virginia Commonwealth University (Richmond, VA), Sussex University (Brighton, England), and the Neuroscience of Addiction conference (Humacao, Puerto Rico).

Dr. Yavin Shaham served as committee member in a study section of the French National Funding Agency for Research (ANR).

Dr. Jennifer Bossert, IRP, gave an invited lecture at the Dopamine Conference in Sardinia and also received the NIDA-IRP mentor award.

Dr. Geoffrey Schoenbaum, IRP, has given several invited lectures in the past three months, including a special Master's Lecture at the University of Amsterdam.

Wilson M. Compton, M.D., M.P.E., DESPR, presented on "Illicit drug outcomes at 3 years in a large national sample in the USA" at the International Federation of Psychiatric Epidemiology, Leipzig, Germany, June 7, 2013.

Dr. Wilson M. Compton chaired the meeting and presented the keynote "The science of addiction: an introduction" in the Substance Addictions & Their Brain Reward Systems Drugs, Alcohol & Nicotine High-Level Science for Policy Consultation Event, Brussels, Belgium, June 3-4, 2013.

Dr. Wilson M. Compton presented a plenary lecture on "Prescription Drug Abuse" in the Regional Meeting for Drug Abuse Demand Reduction, Riyadh, Saudi Arabia, April 30-May 2, 2013.

Dr. Wilson M. Compton chaired a panel and presented on "Funding opportunities at the NIH" as part of the International Conference on Global Health: Prevention and Treatment of Substance Use Disorder and HIV, Taipei, Taiwan, April 17-19, 2013.

Dr. Meyer Glantz, Ph.D. attended the 2013 World Mental Health Consortium meeting as NIDA's representative and scientific collaborator. The WHO meeting was held in Mackinac Island Michigan from July 9 through July 14, 2013. Dr. Glantz collaborates with the Drug Dependence, Nosology, and PTSD analysis workgroups. The WMH Consortium is a multinational set of coordinated community psychiatric epidemiology surveys. The U.S. implementation was the National Comorbidity Survey Replication Survey. Dr. Glantz led discussions on the relationship of substance use to the symptoms, course and outcome of PTSD and the relationship of early stress to development and vulnerabilty.

On April 14, 2013, Dr. Peter Hartsock, DESPR, participated in the release of the Bilateral Presidential Commission (BPC) on the U.S. and Russia's release of the BPC report on U.S.-Russian cooperation in health held in Washington, D.C. The report took two years to produce and NIDA-supported work on drug abuse and MDR TB in Russia received special attention.

Dr. Phil Skolnick, DPMCDA, attended the International Behavioral Neuroscience Society (IBNS) meeting as an invited keynote speaker in Malahide, County Dublin, Ireland, June 25-30, 2013. The presentation was entitled: "Developing Medications to Treat Substance Use Disorders: Pitfalls and Promises."

Dr. Ivan Montoya, DPMCDA, was invited to attend and give a plenary lecture at the International Congress of Addictology Meeting in Paris, France, June 6-7, 2013. The title of his presentation was: *Drugs Today and Tomorrow: Expected Benefits.* He was also an invited presenter at the Dual Diagnosis and Criminal Justice Interventions, in London, England, June 10-11, 2013. The title of his presentation was: *New Pharmacological Interventions.* He met with the British Crime Reduction Initiative (CRI) representatives the day before the meeting in London on June 9th.

The 2013 International Conference on Global Health: Prevention and Treatment of Substance Use Disorders and HIV was held April 17-19, 2013 in Taipei, Taiwan. NIDA CCTN Staff participated in the following:
1) Dr. Betty Tai chaired a session on Medication Assisted Therapy for Opioid Addiction and presented a talk titled "Treating addiction as a chronic condition." Drs. Andrew J Saxon and Walter Ling of the CTN Pacific Region Node were also speakers at this session.

2) Dr. Betty Tai participated as a panel discussant during the brainstorming session on Network and International Collaboration on Substance Abuse and HIV: Consortium of Institutes on Prevention and Treatment of Substance Abuse & HIV in the Asian Region (CIPT-SAHIV-Asia).

Dr. Joseph Frascella, DCNBR, was invited to the University of British Columbia to participate in its Summer Institute on Addiction. He gave a presentation entitled "Some Current Perspectives on Addiction(s)". He also gave a seminar for the faculty of the University of British Columbia entitled "Addiction and the Brain: Some Food for Thought", Vancouver, BC, Canada, July 17 and 18, 2013.

Dr. Vishnu Purohit and Dr. Rao Rapaka, DBNBR, organized a symposium on Cannabinoid CB_2 Receptors in the Brain: Role in Addiction and Psychiatric Disorder at the International Cannabinoid Research Society (ICRS) Meeting, Vancouver, Canada, June 21-26, 2013.

Dr. Rao Rapaka chaired "NIDA INFO Session" at the International Cannabinoid Research Society (ICRS) 2013 meeting and made a presentation on research gaps and future research directions in the research areas of TRP channels, cannabinoids and bioactive lipids.

PROGRAM ACTIVITIES/FOAS

New NIDA RFAs

On May 3, 2013, NIDA issued an RFA entitled **Substance Use Disorders and Molecular Regulation of Brain Energy Utilization RFA-DA-14-006 (R21), RFA-DA-14-005 (R01).** This RFA will support projects investigating the interplay between molecular regulation of brain energy utilization and brain and/or behavioral changes resulting from chronic exposure to abused substances. Open date: July 15, 2013. Application due date(s): August 15, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 15, 2013, by 5:00 PM local time of applicant organization.

On May 30, 2013, NIDA issued an RFA entitled **FY14 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-14-008**. The purpose of this RFA is to support individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. Open date: October 6, 2013. Application due date(s): November 6, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 6, 2013, by 5:00 PM local time of applicant organization.

On May 31, 2013, NIDA issued an RFA entitled **Seek, Test, Treat, and Retain Data Harmonization Coordinating Center (U01) RFA-DA-14-007**. This RFA solicits applications for a single interdisciplinary Coordinating Center to support data harmonization and analysis activities for a subset of NIDA-funded HIV services research grants. Open date: July 16, 2013. Application due date(s): August 16, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 16, 2013, by 5:00 PM local time of applicant organization.

On June 10, 2013, NIDA issued an RFA entitled **Comorbid HIV, Chronic Pain, and Substance Use among Older Adults (R21) RFA-DA-14-012**. This RFA invites innovative, exploratory research applications proposing to study the intersection of HIV, chronic pain, and substance use among older adults. Open date: October 15, 2013. Application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 15, 2013.

On June 10, 2013, NIDA issued an RFA entitled **Integrating Substance Abuse Prevention and Treatment within HIV/AIDS Service Delivery Settings (R01) RFA-DA-14-011**. This RFA encourages hypothesis-driven research project applications to test implementation strategies for integrating evidence-based substance abuse services with HIV care in prevention-oriented settings (including sexually-transmitted infection [STI] clinics) where screening for drug and alcohol problems can be integrated with screening for HIV and other conditions. Open date: October 15, 2013. Application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 15, 2013.

On June 10, 2013, NIDA issued an RFA entitled **HIV/AIDS and Substance Use among Black/African American Women and Young MSM (R01) RFA-DA-14-010**. This RFA seeks R01 research grant applications 1) to conduct research that expands our understanding of the intersection between substance use and HIV among Black/African American women (BAAW) and young Black/African American men who have sex with men (YBAAMSM), and 2) to develop and test interventions that improve HIV prevention and care among BAAW and YBAAMSM, with attention to substance use and its consequences. Open date: October 15, 2013. Application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization.

On June 10, 2013, NIDA issued an RFA entitled **HIV/AIDS and Substance Use Among the Homeless and Unstably Housed (R01) RFA-DA-14-009**. The RFA encourages studies on the development, implementation, evaluation, and dissemination of effective HIV-prevention interventions, research related to the epidemiology of HIV infection and substance use, and health services studies to improve the quality of substance use prevention and treatment services for the homeless and unstably housed populations. Open date: October 15, 2013. Application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 15, 2013, by 5:00 PM local time of applicant organization.

On July 16, 2013, NIDA issued an RFA entitled **Abuse-Resistant and Abuse-Deterrent Formulations and Devices to Avoid the Abuse, Misuse and Diversion of Prescription Opioids by Patients (SBIR)(R43/R44) RFA-DA-14-013**. This RFA represents a focused effort of NIDA on preventing diversion and misuse of prescription opioids at the patient level. Among potentially important steps towards the goal of safer opioid analgesics are the efforts to reformulate medication so that an individual would not be able (abuse resistance) or would not want (abuse deterrence) to divert the prescription drug, and to create innovative medication dispensing devices/gadgets. Open date: September 11, 2013. Application due date(s) October 11, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): October 11, 2013.

New NIDA Program Announcements

On May 6, 2013, NIDA issued a PAR entitled **NIDA Research "Center of Excellence" Grant Program (P50) PAR-13-222**. This PAR provides support for research Centers that (1) conduct drug abuse and addiction research in any area of NIDA's mission, (2) have outstanding innovative science, (3) are multidisciplinary, thematically integrated, synergistic, and (4) serve as national resource(s) to provide educational and outreach activities to drug abuse research communities, educational organizations, the general public, and policy makers in the NIDA research fields. Open date: August 24, 2013. Application due date(s): September 25, 2013, September 25, 2014, September 25, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): January 7, 2014, January 7, 2015, January 7, 2016, by 5:00 PM local time of applicant organization.

On July 3, 2013, NIDA issued a PAR entitled **NIDA Program Project Grant Applications (P01) PAR-13-259**. This PAR supports collaborative research by multi-disciplinary teams which is of high priority to NIDA and leads to synergistic outcomes based on the synthesis of multiple research approaches. Open date: August 25, 2013. Application due date(s): Standard dates, by 5:00 PM local time of applicant organization. AIDS Application due date(s): Standard dates, by 5:00 PM local time of applicant organization.

On July 11, 2013, NIDA issued a PAR entitled **Grand Opportunity in Medications Development for Substance Use Disorders (U01) PAR-13-270.** The purpose of this PAR is to accelerate the development of medication for the treatment of Substance-Use Disorders (SUDs) by encouraging research applications to support a diverse array of preclinical and/or clinical research projects. Open date: February 27, 2014. Application due date(s): March 27, 2014, July 28, 2014, March 27, 2015, July 28, 2015, March 28, 2016, July 28, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): 05/07/2014, 09/07/2014, 05/07/2015, 09/07/2015, 05/07/2016, 09/07/2016, by 5:00 PM local time of applicant organization.

On August 19, 2013, NIDA issued a PAR entitled **Strategic Alliances for Medications Development to Treat Substance Use Disorders (R01) PAR-13-334.** The purpose of this PAR is to support research that advances compounds towards FDA approval by leveraging NIDA funds with the strengths and resources of outside organizations, such as for-profit and not-for-profit entities, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses. Open date: February 27, 2014. Application due date(s): March 27, 2014, July 28, 2014, March 27, 2015, July 28, 2015, March 28, 2016, July 28, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): May 7, 2014, September 7, 2014, May 7, 2015, September 7, 2015, May 7, 2016, September 7, 2016, by 5:00 PM local time of applicant organization.

New FOAs Issued By Collaborative Research On Addiction at NIH (CRAN)

On July 15, 2013, NIDA in collaboration with numerous other NIH components issued an RFA entitled **Revision Applications to Promote Collaborative Research on Addiction at NIH (CRAN): Comorbidity-Related Research (R01) RFA-DA-14-014**. The purpose of this RFA is to notify Program Directors/Principal Investigators (PDs/PIs) that funds are available for revisions to augment existing R01 research projects in order to help meet the goals of Collaborative Research on Addiction at NIH (CRAN); namely, the support of research in cross-cutting areas of substance use, abuse, addiction and related health consequences. Open date: August 24, 2013. Application due date(s): September 24, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): September 24, 2013, by 5:00 PM local time of applicant organization.

On July 15, 2013, NIDA in collaboration with numerous other NIH components issued a PA entitled **Administrative Supplements to Promote Collaborative Research on Addiction at NIH (CRAN): Comorbidity-Related Research (Admin Supp) PA-13-275**. The purpose of this PA is to notify Program Directors (PDs)/Principal Investigators (PIs) that funds are available for administrative supplements to parent awards (see the Activity Code(s) listed

above) in order to help meet the goals of Collaborative Research on Addiction at NIH (CRAN); namely, the support of research in cross-cutting areas of substance use, abuse, addiction and related health consequences. Open date: August 24, 2013. Application due date(s): September 24, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

New FOAs Issued by the NIH Roadmap

On July 26, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Transformative Research Awards (R01) RFA-RM-13-008**. This RFA complements NIH's traditional, investigator-initiated grant programs by supporting individual scientists or groups of scientists proposing groundbreaking, exceptionally innovative, original and/or unconventional research with the potential to create new scientific paradigms, establish entirely new and improved clinical approaches, or develop transformative technologies. Open date: September 4, 2013. Application due date(s): October 4, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 7, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Health Care Systems Research Collaboratory - Demonstration Projects for Pragmatic Clinical Trials Focusing on Multiple Chronic Conditions (UH2/UH3) RFA-RM-13-012.** The purpose of this RFA is to solicit applications for cooperative agreements for Demonstration Projects for efficient, large-scale pragmatic clinical trials focused on management of patients with multiple chronic conditions. Open date: November 2, 2013. Letter of intent due date(s): November 2, 2013. Application due date(s): December 2, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): December 2, 2013, by 5:00 PM local time of applicant organization.

On August 7, 2013, the NIH Common Fund issued a Roadmap RFA entitled **DNA Sequencing Core for an Undiagnosed Diseases Network (UDN) (U01) RFA-RM-13-018.** The purpose of this RFA is to establish a centralized DNA Sequencing Core for Undiagnosed Diseases Network (UDN) patients. Open date: October 19, 2013. Letter of intent due date(s): October 19, 2013. Application due date(s): November 19, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 8, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Director's New Innovator Award Program (DP2) RFA-RM-13-007.** This RFA supports a small number of early stage investigators of exceptional creativity who propose bold and highly innovative new research approaches that have the potential to produce a major impact on broad, important problems in biomedical and behavioral research. Open date(s): September 25, 2013, September 17, 2014, and September 16, 2015. Letter of intent due date(s): Not applicable. Application due date(s): October 25, 2013, October, 17, 2014, and October 16, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 8, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Pioneer Award Program (DP1) RFA-RM-13-006.** The NIH Pioneer Award initiative complements

NIH's traditional, investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose pioneering and possibly transforming approaches to addressing major biomedical or behavioral challenges that have the potential to produce an unusually high impact on a broad area of biomedical or behavioral research. Open date(s): September 18, 2013, September 10, 2014, and September 9, 2015. Letter of intent due date(s): Not applicable. Application due date(s): October 18, 2013, October 10, 2014, and October 9, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 14, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Director's Early Independence Awards (DP5) RFA-RM-13-009.** The NIH Director's Early Independence Award Program supports exceptional investigators who wish to pursue independent research directly after completion of their terminal doctoral/research degree or clinical residency, thereby forgoing the traditional post-doctoral training period and accelerating their entry into an independent research career. Open date(s): December 31, 2013. Letter of intent due date(s): December 31, 2013. Application due date(s): January 31, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Library of Integrated Network-Based Cellular Signatures (LINCS): Perturbation-Induced Data and Signature Generation Centers (U54) RFA-RM-13-013.** This FOA seeks to fund large-scale data production efforts that will enhance the existing LINCS resource while addressing the following: use of a broader range of cell types and assays than used in the existing LINCS resource, improved multidimensional data integration, some new technology development, user-interfaces needed by the typical biomedical scientist, and dissemination of the LINCS approach to study a broad range of disease biology and mechanisms. The outcomes of the research solicited by this FOA are expected to be highly synergistic with those of other research programs. Letter of intent due date(s): November 19, 2013. Application due date(s): December 19, 2013. AIDS application due date(s): Not applicable.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

On May 3, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Short Courses on Innovative Methodologies in the Behavioral and Social Sciences (R25) RFA-OD-13-009**. This RFA invites Research Education Grant (R25) applications to develop, implement, evaluate and disseminate short courses in innovative methods for behavioral and social sciences research (BSSR). Methodological domains include but are not limited to experimental design, data collection, measurement, and data analysis and visualization. Open date: (New Date **October 14, 2013** per NOT-OD-13-073), originally June 3, 2013. Letter of Intent due date(s): (New Date **October 14, 2013** per NOT-OD-13-073), originally June 3, 2013. Application due date(s): (New Date **November 14, 2013** per NOT-OD-13-073), originally July 3, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): (New Date **January 7, 2014** per NOT-OD-13-073), originally July 3, 2013, by 5:00 PM local time of applicant organization.

On May 6, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Integration and Analysis of Diverse HIV-Associated Data (R03) RFA-MH-14-200.** This RFA aims to stimulate the integration of data across HIV research networks and cohorts as well as the development, adaptation and application of state-of-the-art analytic methods to achieve a better understanding of the various factors that characterize neurobehavioral and psychosocial functioning of people living with HIV or those at risk for HIV. Open date: July 19, 2013. Letter of Intent due date(s): July 19, 2013. Application due date(s): August 19, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 19, 2013, by 5:00 PM local time of applicant organization.

On May 17, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Research on the Role of Epigenetics in Social, Behavioral, Environmental and Biological Relationships, throughout the Life-Span and across Generations (R21) RFA-TW-13-002**. This RFA encourages exploratory and developmental grant applications to lay the foundation for innovative and collaborative basic research on the role of epigenetics in social, behavioral, environmental and biological relationships, throughout the life-span and across generations. Open date: October 13, 2013. Letter of Intent due date(s): October 13, 2013. Application due date(s): November 13, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 13, 2013, by 5:00 PM local time of applicant organization.

On June 19, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Person-Centered Outcomes Research Resource (U2C) RFA-CA-13-008.** The purpose of this RFA is to support the creation of a research resource infrastructure for the administration of research investigations using person-centered health outcomes, further referred to as the Person-Centered Outcomes Research Resource (PCORR). The overarching goal for the PCORR will be to facilitate person-centered outcome research by supporting the use and enhancements of the following four measurement information systems, currently funded as separate NIH programs: the Patient Reported Outcomes Measurement Information System® (PROMIS®: http://www.nihpromis.org/); the NIH Toolbox for Assessment of Neurological and Behavioral Function (NIH Toolbox: http://www.nihtoolbox.org/); the Quality of Life (QOL); Outcomes in Neurological Disorders (Neuro-QOL: http://www.neuroqol.org/); and the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me: http://www.air.org/files/4_pager_AIR_Health_Polict_2011_V10F.pdf). Open date: August 26, 2013. Letter of Intent due date(s): August 26, 2013. Application due date(s): September 26, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

On July 1, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Health Services and Observational Studies of Non-Pharmacological Approaches to Managing Pain and Co-Morbid Conditions in U.S. Military Personnel, Veterans, and their Families (R01) RFA-AT-14-005**. This RFA seeks applications proposing Health Services research or Observational studies focused on the use of non-pharmacological approaches to symptom management for pain and associated problems (e.g., post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), substance use

disorder (SUD), depression, anxiety, and sleep disturbances) among U.S. military personnel and Veterans. Open date: September 11, 2013. Letter of Intent due date(s): September 11, 2013. Application due date(s): October 11, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

On July 1, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Studies of Non-Pharmacological Approaches to Managing Pain and Co-Morbid Conditions in U.S. Military Personnel, Veterans, and their Families RFA-AT-14-003 (Clinical Trials and Interventional Studies - R01), RFA-AT-14-004 (Pilot and Feasibility Studies - R34), RFA-AT-14-005 (Health Services and Observational Studies – R01).** These RFAs seek applications proposing clinical trials/interventional research, preliminary clinical studies or health services research/observational studies focused on non-pharmacological approaches to symptom management for pain and associated problems (e.g., post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), substance use disorder (SUD), depression, anxiety, and sleep disturbances) among U.S. military personnel and Veterans. Open date: September 11, 2013. Letter of Intent due date(s): September 11, 2013. Application due date(s): October 11, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

On July 22, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Centers of Excellence for Big Data Computing in the Biomedical Sciences (U54) RFA-HG-13-009**. This RFA supports Big Data to Knowledge (BD2K) Initiative Centers of Excellence to conduct research advancing the science and utility of Big Data in the context of biomedical and behavioral research, and to create innovative new approaches, methods, software, tools, and related resources. Open date: not applicable. Letter of Intent due date(s): October 20, 2013. Application due date(s): November 20, 2013. AIDS application due date(s): November 20, 2013.

New PAs Issued with Other NIH/HHS Components in which NIDA is a participant

On May 30, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Reissue PHS 2013-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42]) PA-13-235**. This PA reissued by the National Institutes of Health (NIH) invites eligible United States small business concerns (SBCs) to submit Small Business Technology Transfer (STTR) grant applications. Open date: July 5, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On May 30, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Reissue PHS 2013-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) PA-13-234**. This PA reissued by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and the Administration for Children and Families (ACF) invites eligible United States small

business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. Open date: July 5, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On May 31, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Native American Research Centers for Health (NARCH) (S06) PAR-13-239**. The purpose of this PAR is to encourage grant applications for new or continued Native American Research Centers for Health (NARCH). The NARCH program supports opportunities for conducting research and research training to meet the needs of American Indian/Alaska Native (AI/AN) communities. Open date: not applicable. Letter of Intent due date(s): July 6, 2013. Application due date(s): August 6, 2013. AIDS application due date(s): not applicable.

On July 24, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R21) PAR-13-282**. This PAR invites research grant applications from organizations/institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. Open date: September 16, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

On August 2, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **NIH Small Research Grant Program (Parent R03) PA-13-304.** This PA supports small research projects that can be carried out in a short period of time with limited resources. The R03 activity code supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. Open date: August 7, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On August 2, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **NIH Exploratory/Developmental Research Grant Program (Parent R21) PA-13-303.** The R21 activity code is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research. Open date: August 7, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS

application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On August 2, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research Project Grant (Parent R01) PA-13-302**. The Research Project Grant (R01) supports a discrete, specified, circumscribed project to be performed by the named investigator(s) in areas representing the specific interests and competencies of the investigator(s). The proposed project must be related to the programmatic interests of one or more of the participating NIH Institutes and Centers (ICs) based on descriptions of their programs. Open date: August 7, 2013. Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On August 2, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01) PA-13-292 (R21) PA-13-288.** This PA encourages behavioral and social science research on the causes and solutions to health and disabilities disparities in the U.S. population. Emphasis is placed on research in and among three broad areas of action: 1) public policy, 2) health care, and 3) disease/disability prevention. Particular attention is given to reducing "health gaps" among groups. Open date(s): September 5, 2013 (**PA-13-292**) September 16, 2013 (**PA-13-288**). Letter of Intent due date(s): not applicable. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On August 8, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Increased Knowledge and Innovative Strategies to Reduce HIV Incidence–iKnow Projects (R01) PAR-13-323.** The purpose of this PAR is to promote innovative research that addresses one or both of the following objectives: 1) Devise optimal strategies to improve the identification of persons unaware of their HIV-1 infection and successfully link them to HIV testing, treatment, and prevention interventions. 2) Develop and examine the feasibility and acceptability of novel integrated interventions of biomedical and behavioral strategies that substantially reduce the likelihood of onward HIV transmission in these populations. Open date(s): December 7, 2013. Letter of Intent due date(s): not applicable. Application due date(s): January 7, 2014; January 7, 2015; January 7, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): January 7, 2014; January 7, 2015; January 7, 2016, by 5:00 PM local time of applicant organization.

New NIH FOAs Issued in Collaboration with the FDA Center for Tobacco Products

On June 20, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Tobacco Control Regulatory Research RFA-OD-13-012 (R03) RFA-OD-13-011 (R01) RFA-OD-13-010 (R21).** The purpose of this RFA is to encourage biomedical, behavioral, and social science research that will inform the development and evaluation of regulations on tobacco product manufacturing, distribution, and marketing. Open date:

December 15, 2013. Letter of Intent due date(s): December 15, 2013; May 17, 2014; December 16, 2014. Application due date(s): January 15, 2014; June 17, 2014, January 16, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

On June 28, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Tobacco Control Regulatory Research RFA-OD-13-016 (K99/R00 Pathway to Independence Award), RFA-OD-13-014 (K01 Mentored Research Scientist Career Development Award), RFA-OD-13-015 (K22 Transition Career Development Award), RFA-OD-13-013 (K08 Mentored Clinical Scientist Research Career Development Award).** The purpose of these RFAs are to increase and maintain a strong cohort of new and talented independent investigators conducting research that will inform the development and evaluation of regulations on tobacco product manufacturing, distribution, and marketing. Open date: September 2, 2013. Letter of Intent due date(s): September 2, 2013. Application due date(s): October 2, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): not applicable.

Other Program Activities

CTN Update

A total of 52 protocols have been initiated since 2001, including multi-site clinical trials (38), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Over 16,000 participants have been enrolled in CTN studies.
Information on protocols can be found at:
http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies

Administrative Research Supplement Update

In the spring of 2012, three grantees were funded administrative research supplements in response to the RFA titled "Adolescent Substance Use Screening Tool Development and Validation for U.S. General Medical and Dental Settings" (DA-12-002). The project was completed on time, and the grantees—Drs. John Knight/Richard Saitz, Sharon Levy and Robert Schwartz—presented their main findings to NIDA staff in July 2013. They have submitted abstracts to AMERSA to present their findings at the November 2013 conference to a larger scientific audience, and manuscripts are to be submitted for journal review in Fall 2013.

Albert Avila, Ph.D., Acting Director, Special Populations Office, coordinated the **17th Annual Summer Research with NIDA program**, which was a huge success. NIDA received over 300 applications from highly qualified high school and undergraduate students. A total of 64 applicants were awarded a research internship and placed with NIDA funded investigators across the U.S. to gain experience in substance abuse-related research. Interns worked on projects in basic, behavioral, clinical and/or epidemiological research areas. Interns in this year's program included: 7 Native Americans, 18 African Americans, 20 Hispanics, 11 Asians, 7 Caucasians, and one biracial awardee.

Pamela Goodlow, Public Health Analyst, Special Populations Office, coordinated the **2013 *"*Research Supplements to Promote Diversity in Health-Related Research" (Diversity Supplements) program.** During FY 2013, NIDA funded 30 new diversity supplement awards from over 40 applications received. Diversity supplements provide recipients with intensive research training and mentoring from NIDA-funded investigators in their lab settings, across all areas of substance abuse research. Awards were made to recipients at the following levels: undergraduate (2), predoctoral (12), postdoctoral (6), and investigator (10). Recipients represented the following ethnic/minority categories: African American (10), Hispanic (16), Pacific Islander (2), Native American (1), and Asian American (1).

On May 7, 2013, Dr. Mary Kautz, DCNBR, participated in a trans-NIH joint Review Policy Committee / Program Leadership Committee Retreat on the NIH Campus, Bethesda, MD. The theme of the retreat was **"Optimizing Program and Review Interactions and Processes across Each Phase of the Grant Cycle"** and was the culmination of efforts from various Workgroups that had been created to prepare preliminary ideas, and had met for several months, prior to the Retreat. Dr. Kautz was a member of the combined "Referral" and "Review" Workgroup, with the goal of identifying areas where Program and Review Staff might improve interactions and work more effectively together as a team to further the NIH mission.

COLLABORATIVE RESEARCH ON ADDICTION AT NIH (CRAN) ACTIVITIES

NIDA and NIAAA co-sponsored the collaborative workshop **"Building the Next Generation of Integrative Approaches for Understanding Comorbid Alcohol, Drug Abuse, and Attention Disorders"** on May 13-14, 2013 in Rockville, MD. The meeting focused on understanding developmental pathways involved in risk for alcohol use and drug abuse disorders for comorbid sub-populations and the development of integrative models of risk and novel approaches that may be more generalizable to health care providers, researchers, and policy makers. Drs. Karen Sirocco, NIDA, Cheryl Anne Boyce, NIDA, and Mariela Shirley, NIAAA, served as the joint institute co-chairs of this meeting.

On March 13, 2013, NIDA, in conjunction with NIAAA, NICHD, NIMH and NINDS, held **"Views By Two: Addressing Health Disparities Through Neuroscience"** with speakers Drs. Guillermo Bernal (University of Puerto Rico) and Patricia Molina (Louisiana State University Health Sciences Center), who presented on the topic "Is Evidence-Based Medicine Generalizable to all Races and Ethnicities?" The goal of the series is to increase awareness of health disparities relating to neuroscience through a collegial discussion between 2 renowned scientists on a shared topic. Flair Lindsey, Program Analyst, Special Populations Office, represents NIDA on this inter-agency planning committee.

Ivan Montoya, Medical Officer of NIDA DPMC was re-appointed Chair of the Addictions IRB, which serves the Intramural Research Programs of NIDA and NIAAA.

COMMUNICATIONS

PUBLICATIONS/VIDEOS

NIDA Publications and Online Resources

NIDA Notes (now online only)

Thirteen new articles have been posted on the NIDA Notes homepage. These articles included the first NIDA@Work video, featuring Redonna Chandler, PhD., Health Services Research Branch. The NIDA Notes Glossary was activated, allowing readers to click on hyperlinks to get definitions of technical terms used in the newsletter.

Videos

- NIDATV Scientist Spotlight (Dr. D'Annu)
http://www.youtube.com/watch?v=KVW7euSLZns
- Emerging Drugs- Methylone and Molly
http://www.youtube.com/watch?v=lBwBioVwkCY
- NIDATV Scientist Spotlight (Dr. Steffanie Strathdee)
http://www.youtube.com/watch?v=B7xdBAzpgPw
- NIDATV Scientist Spotlight (Dr. Richard Spoth)
http://www.youtube.com/watch?v=XsEWk9tAm8c
- NIDATV Scientist Spotlight (Dr. Redonna Chandler)
http://www.youtube.com/watch?v=ud_dNRlFnsw
- Assisted with production of Childmind Institute's video to promote Dr. Volkow's talk May 6, 2013
- Friends of NIDA, Congressional Briefing: Substance Abuse and the Military Community Brief http://www.youtube.com/watch?v=R24FNB5F6fg
- Addiction Performance Project (APP) Online (Three products) http://www.youtube.com/watch?v=8Wx3K14gQfk, http://www.youtube.com/watch?v=HSUX_qv8TdY, and http://www.youtube.com/watch?v=zBLzbAKhnVo
- What's New at NIDA video promo http://www.youtube.com/watch?v=Tyw4yLw8aVo

CTN-Related Publications

Six editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 27 CTN studies are now available on the NIDA Data Sharing website http://www.nida.nih.gov/CTN/Data.html. Over 2,000 data sets have been downloaded by researchers from 45 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience

Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

International Program-Related Publications/Online Initiatives

NIDA International Program E-News

- *June 2013* – This issue highlighted the binational agreement between NIDA and Inserm, collaboration between the Mexican Instituto Nacional de Psiquiatria Ramón de la Fuente and the CTN Florida Node Alliance, and a new IP webinar that explores the role of research in drug policy. Other stories reported on the impact of NIDA- and Fogarty International Center-funded research in Bulgaria, and graduation ceremonies for NIDA Hubert H. Humphrey Drug Abuse Research Fellows at Virginia Commonwealth and Johns Hopkins universities.
- *April 2013* – The E-News described new funding opportunities and the participation of NIDA Director Nora D. Volkow, M.D., in a roundtable discussion by National Institutes of Health leaders during the Consortium of Universities for Global Health conference, held March 14–16, 2013, in Washington, DC. Other stories summarized drug abuse research efforts in Saudi Arabia that include NIDA grantees, presentations by NIDA fellows at the March 14 CTN Steering Committee Meeting, and the appointment of former INVEST/CTN fellow Amit Chakrabarti, M.D., to the National Institute of Occupational Health in India.

Webinar Explores Role of Research in Drug Policy

The latest NIDA International Program webinar, Understanding the Relationships Between Policy and Research, is now available for viewing. Alison Ritter, Ph.D., who directs the Drug Policy Modelling Program at the University of New South Wales, Australia, provides viewers with a broad overview of the drug policy process. Building on her extensive experience in Australian and international settings, Dr. Ritter focused on the interaction among multiple players—including politicians, the media, and drug abuse researchers—who define drug problems and identify and evaluate potential solutions.

Other Publications by NIDA Staff

Boyce CA, Lynne-Landsman SD. Integrating translational neuroscience to improve drug abuse treatment for adolescents. Psych Addictive Behaviors. 2013; 27(2): 547-555.

Compton WM, Dawson DA, Grant BF. Crosswalk between DSM-IV dependence and DSM-5 substance use disorders for opioids, cannabis, cocaine and alcohol. Drug and Alcohol Dependence 2013 May 1 [Epub ahead of print].

Michel ME, Pintello DA, Subramaniam G. Blending research and practice: an evolving dissemination strategy in substance abuse. Soc Work Public Health. 2013 May; 28(3-4): 302-312.

Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, David Haddox J, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 2013 Jun 20. doi:pii: S0304-3959(13)00329-1. 10.1016/j.pain.2013.05.053. [Epub ahead of print]

Subramaniam GA. Opioid use disorders in adolescents: A review of prevalence, problems, clinical features and treatment options. Adolescent Psychiatry April 3(2): 117-122.

Tai B, Volkow ND. Treatment for substance use disorder: Opportunities and challenges under the Affordable Care Act. Soc Work Public Health. 2013 May; 28(3-4): 165-174.

Weinberg N, Lopez M, Compton WM. Epidemiology of Drug Abuse: Building Blocks for Etiologic Research. In: Madras B (Editor), The Effects of Drug Abuse on the Human Nervous System. Neuroscience-Net, LLC, 2012. Updated June 30, 2013.

Book Chapters

Cocaine and Amphetamine Neuroimaging in Small Rodents. In: Biological Research on Addiction: Comprehensive Addictive Behaviors and Disorders. Stark, J.A., Lu, H. and Stein, E.A. Elsevier Inc., San Diego: Academic Press, pp. 699–710, 2013.

Brain, Reward and Drug Addiction. Pariyadath, V, Paulus, M and Stein, E.A. Brain, Reward and Drug Addiction. In: Charney, D. and Nestler, E (eds). Neurobiology of Mental Illness Oxford, England. 2013.

Dr. John Satterlee, DBNBR, published a book chapter entitled "Epigenomic and Non-coding RNA Regulation in Addictive Processes" in Environmental Epigenomics in Health and Disease Vol 2 Epigenetics and Complex Diseases, edited by Randy Jirtle and Fred Tyson.

COMMUNITY AND PRESS EVENTS

NIDA Participates in ONDCP's Unveiling of 2013 National Drug Control Strategy
On April 24, 2013, ONDCP Director Gil Kerlikowske, Dr. Nora Volkow, and Baltimore Police Commissioner Tony Batts, spoke at a press conference held at Johns Hopkins University School of Medicine regarding ONDCP's release of the 2013 National Drug Control Strategy, the Obama Administration's primary blueprint for drug policy in the United States.

Dr. Volkow Receives ASAM Award
On April 25-28, Dr. Volkow attended the American Society of Addiction Medicine (ASAM) 44th Annual Medical-Scientific Conference in Chicago, Illinois, where she was presented with the John P. McGovern Award. This award was established in 1997 to recognize and honor an individual who has made highly meritorious contributions to public policy, treatment,

research, or prevention which has increased our understanding of the relationship of addiction and society. Dr. Volkow also addressed the gathering with the Lecture on Addiction and Society.

Dr. Nora Volkow participated in the World Science Festival
In May 2013, Dr. Volkow attended the World Science Festival *Pioneers in Science* program where she participated in two town-hall style sessions each with groups of 50 high school students - one in English and the other in Spanish. She was videotaped answering questions from high school students from the New York area, with selected schools around the world tuning in remotely via Google Hangouts. *Pioneers of Science* is an annual program that allows students to interact with world-renowned scientists. The event was moderated by *WABC News,* who also interviewed Dr. Volkow. The previous night, Dr. Volkow participated in *The Moth Mainstage* event in which she was one of five storytellers who told a personal story on the theme *What Lies Beneath: Stories of Discovery*.

Dr. Nora Volkow participated in Child Mind Institute Webinar
On May 6, 2013, Dr. Nora Volkow participated in a Speak Up for Kids video webinar for the Child Mind Institute. She spoke about "*Raising Drug-Free Kids: How Can the Science of Addiction Help Us?*"

Dr. Nora Volkow selected as a Sammies finalist
In June 2013, Dr. Volkow was named one of 31 finalists for the Samuel J. Heyman Service to America Medals, also known as the Sammies, which recognizes outstanding service and are considered among the most prestigious available to federal workers. Dr. Volkow was recognized as a finalist for the "Science and Environment" medal.

Press Releases

May 17, 2013
Study of "screen time" on mood, memory, and cognition wins top NIH Addiction Science Award.
Projects on "bath salts" and the link between fetal alcohol exposure and diabetes take other honors

Science Spotlights and Announcements

May 10, 2013 – *NIDA and AstraZeneca partner to develop potential addiction medication.*
NIDA and AstraZeneca, a global research-based biopharmaceutical company, joined efforts to explore a novel medication to treat drug addiction. The scientific partnership will explore a specific molecule that modulates the activity of glutamate – an excitatory neurotransmitter. Preclinical studies with this class of molecule indicate that it could be effective for treating a range of mental disorders, including abuse of substances ranging from tobacco to cocaine.

May 14, 2013 –*NIDA and INSERM forged a new collaboration on the neuroscience of addiction.* On May 7, NIDA and the Institut National de la Santé et de la Recherche Médicale (INSERM) -- the French scientific and technological institute focusing on human health -- signed a Memorandum of Intent to strengthen cooperation in basic and clinical research and research training, specifically in the areas of neuroscience and psychiatry. François Delattre, French Ambassador to the United States, provided opening remarks on the importance of fostering exchange of scientific information between France and the United States, and also signed the Memorandum of Intent.

May 16, 2013 – *Heroin and cocaine vaccines successful in preclinical studies*. Two recent preclinical studies, published in *PNAS* and *Nature*, have reported successful tests for vaccines to help overcome heroin or cocaine addiction.

June 20, 2013 – *Two studies highlight strategies to reduce teen drug use*. Two studies have reported success in reducing teen drug use. One study examined the effectiveness of specific policies that limit teen access to tobacco products (for example, ID requirements, vending machine restrictions, repackaging restrictions) on smoking in adulthood. The other study explored the effectiveness of a community-based intervention program (PROSPER) in reducing substance abuse in teens up to 6½ years later.

July 1, 2013 - *Special journal edition focuses on integrating brain science with addiction treatment.* The journal, *Psychology of Addictive Behaviors*, published a special issue devoted to NIH-funded research aimed at integrating brain science and addiction treatment research. The articles were organized and co-edited by NIDA and NIAAA grantees Sarah Feldstein Ewing (University of New Mexico) and Tammy Chung (University of Pittsburgh).

July 11, 2013 — *Research partnership launched to improve juvenile justice prevention and treatment services for drug abuse, HIV*. NIDA launched the Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS). As part of this JJ-TRIALS cooperative, seven research centers will work together to determine how juvenile justice programs can effectively adopt science-based prevention and treatment services for drug abuse and HIV.

July 17, 2013 — *Funding Opportunity Announcements for Collaborative Research on Addiction at NIH (CRAN).* NIDA, NIAAA, and NCI announced the release of two new FOAs to promote the goals of Collaborative Research on Addiction at NIH (CRAN; formerly known as functional integration). Its mission is to provide a strong collaborative framework for enabling NIDA, NIAAA, and NCI to pool resources and expertise, creating synergies in addiction science, addressing new research opportunities, and meeting the public's health needs.

August 12, 2013 — *Statement from NIDA Director Nora Volkow on NIDA's commitment to marijuana research.* As part of its mandate to study drug abuse and addiction, and other health effects of both legal and illegal drugs, NIDA funds a wide range of research on and related to marijuana (cannabis); its main psychoactive ingredient, THC; and chemicals related to THC (cannabinoids).

Media Advisories

May 3, 2013
NIDA's Dr. Nora Volkow joins President Clinton on Clinton Foundation's prescription drug abuse panel.
Dr. Nora Volkow, director of NIDA, joined President Bill Clinton, New York dignitaries, and college students from New York University for a panel discussion on prescription drug abuse among 18 – 26 year olds, and how the Clinton Foundation's Clinton Health Matters Initiative can work with others to contribute to solutions in New York and nationwide.

May 7, 2013
Advancing Psychiatric Practice through the Science of Addiction.
NIDA presented a special research track at the American Psychiatric Association's (APA's) 166th annual meeting in San Francisco from May 18 to 22. The NIDA sessions highlighted a wide range of topics to advance psychiatric practice through addiction science.

May 13, 2013
Mare Winningham and Patrick Kennedy join NIDA's Addiction Performance Project.
Movie and television star Mare Winningham led an impressive cast in the Addiction Performance Project, an innovative continuing medical education (CME) program for doctors and other health providers, on May 19 in San Francisco, Calif. The performance is a project of NIDA and is designed to help doctors and other health professionals better identify and help drug-abusing patients in health care settings, and to break down the stigma associated with drug addiction. The performance took place at the annual meeting of the American Psychiatric Association (APA).

Interview Highlights: March 2013 – August 2013

Medscape — Dr. Nora Volkow was interviewed about obesity/compulsive eating and Dr. Wilson Compton was interviewed about addiction research.

The Scientist — Dr. Nora Volkow was interviewed about imaging.

Allure — Dr. Joe Frascella was interviewed about breaking bad habits.

St. Louis Post-Dispatch — Drs. Dave McCann and Redonna Chandler were interviewed about prescription drug abuse.

Science News – Dr. Nora Volkow was interviewed about alcohol.

Epoch Times — Dr. Marilyn Huestis was interviewed about marijuana drug testing.

Trail Runners Magazine – Dr. Marilyn Huestis was interviewed about marijuana.

AP – Dr. Wilson Compton was interviewed about opioids.

What do you think? (Mexico magazine) — Dr. Nora Volkow was interviewed about addiction.

Science Magazine — Dr. Nora Volkow was interviewed about imaging.

Associated Press/Milwaukee — Dr. David Shurtleff was interviewed about pain.
Phoenix New Times — Dr. Marilyn Huestis was interviewed about drugged driving.

Discover Magazine — Dr. Roy Wise was interviewed about addiction

Popular Science — Dr. Wilson Compton was interviewed about opioids.

Telemundo — Dr. Ruben Baler was interviewed about steroids.

Bucks County Courier Times — Dr. Ruben Baler was interviewed about steroids.

Scientific American Mind — Dr. Nora Volkow was interviewed about food/compulsive overeating.

NIH Radio — Dr. Nora Volkow was interviewed about food/compulsive overeating.

Associated Press — Dr. Nora Volkow was interviewed about marijuana.

SciBX – Dr. Nora Volkow was interviewed about obesity.

New York Times – Dr. Nora Volkow was interviewed about overeating/food.

Voice of America — Dr. David Shurtleff was interviewed about vaccines.

National Geographic – Dr. David Shurtleff was interviewed about addiction

Kansas City Star – Dr. Ruben Baler was interviewed about addiction.

WYPR-FM - Dr. George Uhl was interviewed about addiction.

The Fix.com – Dr. Wilson Compton was interviewed about DSM-V.

Los Angeles Times – Dr. Steve Gust was interviewed about prescription drug abuse.

SELF Magazine — Dr. Joe Frascella was interviewed about addiction.

NPR – Dr. Nora Volkow was interviewed about addiction.

Chicago Tribune — Dr. Nora Volkow was interviewed about compulsive overeating.

The Washington Post — Dr. Joni Rutter was interviewed about tobacco/nicotine.

New York Times — Dr. Nora Volkow was interviewed about prescription drug abuse.

AllTreatment.com — Dr. Ruben Baler was interviewed about inhalants.

Wall to Wall TV — Dr. Kenzie Preston was interviewed about heroin research.

Addiction Professional — Dr. Redonna Chandler was interviewed about criminal justice/law.

Health Magazine — Dr. Susan Weiss was interviewed about prescription drug abuse among women.

Frontline Magazine — Dr. Marilyn Huestis was interviewed about designer drugs

Dr. Nora Volkow, Dr. Wilson Compton, Dr. Ivan Montoya, and/or Dr. Geetha Subramaniam were interviewed about the NIDA track at the APA annual meeting by the following outlets:

- *APA Psychiatric News*
- *Join Together*
- *APA Daily Bulletin*
- *Psychiatric Annals.*

Dr. Antonello Bonci and Dr. Billy Chen were interviewed by the following media outlets about their optogenetic research published in *Nature:*

- *Columbia Chronicle*
- *Plain Dealer*
- *The Verge*
- *Sveriges Radio*
- *BioscienceTechnology.com*
- *KQED-FM*
- *Zeit online*
- *Voice of America*
- *Science News Magazine*
- *NewsTalk 7070*
- *Agence France-Press*
- *SINC*
- *La Stampa*
- *KSL-FM*
- *RAI-Radio 3*

MEETINGS/CONFERENCES

The National Institute on Drug Abuse (NIDA) presented a special research track at the **American Psychiatric Association (APA) Annual Meeting in San Francisco, California, May 18-22, 2013.** NIDA participated in a number of sessions on topics unique to addiction science. NIDA Director Nora Volkow gave a Frontiers of Science Lecture on new scientific findings and therapeutic opportunities to address substance use disorders. There were sessions on the clinical implications of changes in the revised DSM-5; comorbid psychiatric and substance use disorders (SUDs) and the implications for early identification and treatment; and advances in pharmacotherapies for SUDs. Symposia and lectures provided an update to participants on areas critical to psychiatric practice, including a session on risk assessment and treatment of cannabis use in youth and another on prescription opioid abuse and treatment options. A special forum of NIDA's *Addiction Performance Project* was also featured at this year's meeting.

The **Annual Meeting of the College on Problems of Drug Dependence (CPDD)** was held June 15-20, 2013, in San Diego, CA. NIDA held a **Grant-Writing and Career Workshop** and the **NIDA/CPDD Training Networking Event**. The Grant-Writing and Career Workshop provided information on NIDA research priorities, program interests and funding opportunities, review procedures, and training on grantsmanship and other career-building skills. Presenters included Drs. David Shurtleff and Kevin Walton, Linda Cottler (University of Florida), Steffanie Strathdee and Thomas Patterson (University of California, San Diego). The Training Networking Event provided a forum for training directors and trainees to learn about NIDA's training programs and for trainees to network with NIDA staff and find future training and employment opportunities. In addition, NIDA's Women & Sex/Gender Differences Research Program awarded 28 **Women & Gender Junior Investigator Travel Awards** to promote entry of junior investigators into drug abuse research on women and sex/gender differences.. NIDA also awarded 20 **Director's Travel Awards** for the National Research Service Award (NRSA) trainees and fellows, and Diversity Supplement recipients to present at the CPDD meeting and attend the NIDA Grant-Writing and Career Workshop.

The National Institute on Drug Abuse (NIDA) organized a program at the **2013 American Psychological Association (APA) Annual Meeting in Honolulu, HI, July 31 – August 4.** A number of NIDA staff were involved in the planning of sessions on a wide range of topics related to addiction research. NIDA also co-sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

ASAM Annual Conference: In collaboration with ASAM, NIDA was instrumental in organizing and presenting several symposia on important topics at this year's annual conference in Chicago, April 25-28, 2013. (1) Dr. Jag Khalsa of DPMCDA, Dr. Geetha Subramanian, CCTN, and Dr. Gavin Bart of ASAM presented on "**Buprenorphine: New Formulations, Medication Combinations, Indications and Longitudinal Effects**"; (2) Dr. Khalsa and Dr. Marc Galanter, ASAM, and in collaboration with ISAM, organized/presented on "**International Perspectives on Addiction Medicine**"; (3) Dr. Khalsa and Dr. Jeffrey Samet of ASAM presented on "**Addressing Care for Hepatitis C Virus Infection I the**

Addicted Patient: The Dawn of a New Era in Screening and Treatment"; and (4) Dr. Khalsa, Dr. Guifang Lao and Dr. Shwe Gyaw of DPMCDA presented on **"Substance Abuse and Post-Traumatic Stress Disorder (PTSD): Chicken first or an Egg?"**.

On April 25-26, 2013, NIDA's Special Populations Office hosted a two-day **Special Populations Research Development Seminar Series workshop** in Bethesda, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 10 new substance abuse investigators and NIDA-supported faculty mentors in an intensive grants development workshop setting, and culminated in a mock review of research grant applications submitted by the new investigator participants.

Drs. Jessica Chambers and Lisa Onken, DCNBR, held a NIDA-sponsored meeting on **Future Directions for Developing Behavioral Treatments for Adolescent Drug Abuse,** which was held on June 11-12, 2013, in Rockville, MD**.** The primary focus of this meeting was on improving the community-friendliness of existing evidence based treatments and the next generation of adolescent drug abuse treatments.

Dr. Yu (Woody) Lin of DCNBR organized a symposium entitled "**fMRI-based Biomarkers for Clinical Pain and Analgesia",** held at NIDA on June 27, 2013. It was co-sponsored by DCNBR, the NIDA Prescription Opioid and Pain Workgroup, and the NIH Pain Consortium.

Dr. Vishnu Purohit and Dr. Rao Rapaka, DBNBR, organized a NIDA symposium on the **Role of Cannabinoids in Drug Addiction** at NSC, Rockville, Maryland, July 11-12, 2013.

Drs. Rao Rapaka and Vishnu Purohit, DBNBR, organized a conference entitled **"TRPs as Probes and Medications for CNS Disorders: Focus on the Trptome, Trptomics, Addiction and Pain"** at the NSC building, for DBNBR/NIDA on July 29, 2013.

Drs. Rao Rapaka, Vishnu Purohit and Hari Singh, DBNBR, organized a conference entitled **"Emerging trends in the Abuse of Designer Drugs and Their Catastrophic Health Effects: Update on Chemistry, Toxicology, Addiction Potential and Treatment"** at the NSC building, for DBNBR/NIDA on July 26, 2013.

On June 12, 2013, Dr. Jack Stein, Director, OSPC, gave a webinar plenary at Aetna's 2013 BH Summit on Opioid Drug Abuse entitled "Prescription Drug Abuse: It's Not What the Doctor Ordered."

On June 20, 2013, Dr. Jack Stein, Director, OSPC, was a panelist at ASAM's Advancing Access to Addiction Medications Stakeholder's Summit at the National Press Club in Washington, DC.

On May 17, Dr. Ruben Baler, Science Policy Branch, OSPC, gave a Keynote Address entitled: "Where do addictions come from?" at the 2013 Annual Luncheon of the national Council on Alcoholism and Drug Dependence, Rochester, NY.

On June 4, 2013, Dr Baler gave a presentation and Q&A session on "The Brain" to 5th graders at Rosemont Elementary School in Gaithersburg, MD.

On July 24, 2013, Dr. Baler led a workshop on "The Neuroscience of Addiction, risk, vulnerability and effects" to agents and staff from the Drug Enforcement Agency (DEA), Quantico, VA.

Drs. Skolnick, Montoya and Hampson, DPMCDA, attended and participated in the 53rd NCDEU Annual Conference in Hollywood, FL, May 28-31, 2013.

Dr. Montoya attended and participated in the American Psychiatric Association (APA) Annual Meeting, in San Francisco, CA, May 18-22, 2013.

Dr. Shou Ha Li, DPMCDA, attended and participated in the 22nd Annual ICSA Applied Statistical Symposium and the 3rd ISBS International Symposium on Biopharmaceutical Statistics, which were held jointly from June 9-12, 2013 in Bethesda, MD.

Dr. Nathan Appel, DPMCDA, presented a seminar on the role of preclinical toxicology and safety pharmacology in drug discovery and unique issues concerning potential medications to treat stimulant abuse to KUMC toxicology graduate students on May 14-15, 2013, in Kansas City, KS.

Dr. Appel attended the 12th World Pharma Congress (WPC) Conference from June 2-5, 2013, Philadelphia, PA. He took 3 courses during this conference, "Utilization of Cardiac Contractility Assays for Preclinical Safety Testing" and "Introduction to Drug Metabolism and its Role in Drug Toxicity" on 6/3 and "Integrated Drug Safety Risk Assessments Meeting" on June 4, 2013.

Drs. David McCann, Jane Acri and Kevin Walton, DPMCDA, attended and participated in the College on Problems of Drug Dependence (CPDD) Meeting in San Diego, CA, June 15-20, 2013.

Drs. David McCann and Jane Acri also attended and presented at the ISGIDAR meeting before CPDD.

Dr. John Satterlee, DBNBR, gave a presentation entitled "Overview of the Common Fund Epigenomics Program" to the NIH DPCPSI Council of Councils on May 14, 2013.

Dr. John Satterlee organized an NIH-wide presentation by Dr. John Stamatoyannopoulos entitled "A Roadmap to the Living Genome" which took place in Natcher Auditorium, on May 15, 2013.

David A. Thomas, Ph.D., DBNBR, made a presentation to the Interagency Pain Research Coordinating Committee titled "Update on the Evidence-based Methodological Workshop on Chronic Pain and Opioids" June 3, 2013 in Bethesda, MD.

David A. Thomas, Ph.D. made a presentation to the Pain Care Forum titled "NIH Pain Consortium's Centers of Excellence in Pain Education" on June 13, 2013 in Washington, DC.

David A. Thomas, Ph.D. made a presentation to the University of Kansas Center for Practical Bioethics titled "Update on the NIH Pain Consortium's Centers of Excellence in Pain Education" July 11th, 2013 via teleconference.

Dr. Cora Lee Wetherington, DCNBR and Women and Sex/Gender Differences Research Program Coordinator, co-chaired with Dr. Sharon Allen, University of Minnesota, the symposium, "Sex Hormone Modulation of Nicotine Reward: Effects on Urges, Affect, Physiological Response and Brain Activation," at the annual meeting of the College on Problems of Drug Dependence in San Diego, CA, June 15-20, 2013.

Dr. Cora Lee Wetherington co-chaired with Dr. Suzette Evans, Columbia University, the workshop, "Animal Models of Sex Differences & Drug Abuse: Mind the Gaps," at the annual meeting of the College on Problems of Drug Dependence in San Diego, CA, June 15-20, 2013.

Dr. Cora Lee Wetherington gave an invited talk, "Sex Differences in Drug Abuse," at the Society for Women's Health Research's (SWHR), What a Difference an X Makes – The State of Women's Health Research" Conference (X Conference), Washington, DC, July 18-19, 2013.

Dr. Cora Lee Wetherington co-chaired with Dr. Sherry McKee, Yale University School of Medicine, the symposium, "Gender Differences & Substance Abuse Treatment: The Lab, the Clinic & Health Care Reform," at the American Psychological Association 121st Annual Convention, Honolulu, HI, July 31-August 4, 2013.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program, has been invited to co-chair an all-day HHS meeting "Intimate Partner Violence Screening and Counseling: Research Symposium," to be held on October 4, 2013 on the NIH campus. Dr. Noursi is co-chairing this meeting with Dr. Nancy Lee, Deputy Assistant Secretary for Health-Women's Health and the Director, Office on Women's Health/OASH/OS/HHS, along with Dr. Marylouise Kelley, Director of the Family Violence Prevention and Services Program at the Administration on Children and Families. Other participating agencies are ACL, ASPE, AHRQ, CDC, OASH, OPA, OWH, and SAMHSA. Several NIDA grantees are invited to present at the meeting.

Dr. Samia Noursi chaired (with Stephen Higgins), a symposium, "Behavioral Economics and Maternal-Infant Health among Substance Abusers," at the American Psychological Association 121st Annual Convention, July 31-August 4, 2013, Honolulu, HI. The panel included presentations by Warren K Bickel, Ph.D. (Virginia Tech University), Stephen T. Higgins, Ph.D. (University of Vermont), Tricia E. Wright, M.D. (University of Hawaii), & Sarah H. Heil, Ph.D. (University of Vermont).

Dr. Joseph Frascella, DCNBR, gave a presentation as part of a panel entitled, "Leading the Conversation on Food" at the International Food Information Council's Fourth Annual Science Communications Summit in Washington, DC, May 2013.

Dr. Karen Sirocco, DCNBR, served as an invited speaker for the "Advancing Transdisciplinary Translation for Prevention of High-Risk behaviors: Critical Thinking to Overcome Individual and Institutional Barriers" held on April 29, 2013 in Washington, DC. The conference was sponsored by the NIH OBSSR OppNet funded grant to NIDA grantee Dr. Diana Fishbein, Research Triangle Institute (R13NR013623).

On May 28, 2013, Dr. Cheryl Anne Boyce, DCNBR, presented on "NIH Research and Health Disparities" at the Orientation for the RISE-UP and Ferguson Fellowships for underrepresented scholars interested in public health careers at Johns Hopkins University, Baltimore, MD.

Dr. Cheryl Anne Boyce presented on "Strategies for Research Funding" at the 19th Annual Black Graduate Psychology Conference in Chapel Hill, North Carolina held June 7-9, 2013. She also participated in a panel on careers in psychology during the conference for postdoctoral and early career scholars.

At The Robert Wood Johnson Foundation's "New Connections: Increasing Diversity of RWJF Programming- Seventh Annual Symposium" held in Princeton New Jersey, Dr. Cheryl Anne Boyce presented "Debunking Myths and Urban Legends about NIH Grant Funding " as part of this research coaching clinic for underrepresented scholars on June 14, 2013. She also served as one of the speed mentoring faculty on June 13, 2013.

On July 8, 2013, Dr. Cheryl Anne Boyce presented on "NIH: An Overview of Research Opportunities and Careers" to the University of Maryland, Baltimore County Meyeroff Scholars 2013 Summer Orientation.

Dr. Cheryl Anne Boyce presented on "Behavioral and Brain Development Research and Cross-Cutting Initiatives of the NIDA Child and Adolescent Workgroup" at the Adolescent Health Working Group (AHWG) of the Office of Adolescent Health, Office of the Assistant Secretary of Health hosted by NIDA's Prevention Branch, DESPR on July 2, 2013.

Dr. Lisa Onken, DCNBR, moderated a panel on use-inspired basic research at the Third Annual Meeting of Investigators for the Science of Behavior Change (SOBC). Held on June 20-21, 2013, in Bethesda, MD. The meeting included investigators funded under the SOBC initiative, and it also included investigators who were funded to conduct use-inspired basic research under the Pasteur's Quadrant administrative supplement initiative.

Dr. James Bjork, DCNBR, gave a talk entitled "Neurocircuitry of Incentive Processing in Alcoholism and in Adolescents at Risk" on June 26, 2013, as part of a special symposium entitled: "Why We Like To Drink: And Other Lessons on Alcohol from MRI Studies: A Tribute to Dan Hommer!" at the 36th Annual Scientific Meeting of the Research Society on Alcoholism, in Orlando, FL.

Dr. Yu (Woody) Lin, DCNBR, was invited by the American Academy of Pain Medicine to organize and moderate a workshop session entitled "NIH Pain Research: Optimizing Funding through Grant Writing". The conference was held at the society's 29th annual conference, April 11–14, 2013 in Ft. Lauderdale, FL.

Dr. Yu (Woody) Lin and Dr. Scott Kollins of Duke University co-organized a session entitled "Smoking and ADHD Comorbidity: Mechanisms and Clinical Implications". This symposium was NIDA-sponsored. It was held at the 2013 APA Annual Conference, May 18–22, 2013 in San Francisco, CA.

Dr. Yu (Woody) Lin organized a symposium at the NIDA International Forum entitled "AAPI-ACTION: Advancing Clinical Translation, Innovations, Opportunities and Networks". It was a pre-meeting event of 2013 CPDD, held in San Diego, CAa on June 15, 2013.

Dr. Wilson M. Compton, M.D., M.P.E., Director, DESPR, continues to participate in the White House Office of National Drug Control Policy Interagency Workgroup on a continuing basis.

Dr. Wilson M. Compton continues to participate in two interagency workgroups for the Department of Health and Human Services: The Behavioral Health Coordinating Committee (particularly the Prescription Drug Abuse Subcommittee) and the Tobacco Control Steering Committee (including co-chairing the Data/Research Subcommittee) on a continuing basis.

Dr. Wilson M. Compton continues to participate in the NIH Opportunity Network for Basic Behavioral and Social Science Research (OppNet) as a member of the Steering Committee and as an alternate for the Coordinating Committee on a continuing basis.

Dr. Wilson M. Compton completed his work with the American Psychiatric Association (APA) on the DSM-5 Task Force and DSM-5 Substance Use Disorders Workgroup with the publication of DSM-5. He also participated in the Annual Meeting of the APA and presented 2 papers on the DSM-5 development process and chaired a panel on Prescription Opioid Abuse, where he presented a paper on the epidemiology of the problem, May 17-22, 2013.

Dr. Wilson M. Compton presented on "Understanding addiction as a brain disease: judicial interventions to shape behavior" as part of a workshop at the Federal Judicial Center Region 9 Training, San Diego, CA, July 15, 2013.

Dr. Wilson M. Compton presented in a Plenary Federal Panel at the State Associations of Addiction Services National Conference and NIATx Summit, San Diego, CA, July 16, 2013.

Dr. Wilson M. Comptonchaired a symposium on Hepatitis C at the College on Problems of Drug Dependence meeting, San Diego, CA, June 17, 2013.

Dr. Wilson M. Compton presented on "Focusing on drug use in medical settings" at the annual meeting of the ACCME, Chicago, IL, April 25, 2013.

On June 13, 2013, Dr. Redonna K. Chandler, DESPR, Services Research Branch, presented a paper entitled, NIH Research on Screening, Brief Intervention, and Referral to Treatment for Substance Use Disorders at the 2013 NIDA International Forum held during the 75th Annual Meeting of the College on Problems of Drug Dependence, San Diego, CA.

On June 17, 2013, Dr. Redonna K. Chandler presented a paper entitled, Juvenile Justice Research at NIDA: JJ-TRIALS Initiative at the 75th Annual Meeting of the College on Problems of Drug Dependence, San Diego, CA.

On July 12, 2013, Dr. Redonna K. Chandler presented, The Addicted Brain: Sentencing and Post Sentencing Considerations, at the 2013 Ninth Circuit Federal Judicial Center Mid-Summer Workshop, San Diego, CA.

On May 4, 2013, Dr. Harold Perl, DESPR, Prevention Research Branch, gave an invited plenary talk titled "Peeking behind the Curtain of the NIH Funding Process: Tips for Preparing a Successful Grant Application" at the inaugural Collaborative Perspectives on Addiction (CPA) Conference in Atlanta, GA.

On May 9, 2013, Dr. Harold Perl taught a webinar titled, "Peeking behind the Curtain of the NIH Funding Process" at the 19th Annual Convention of the National Association of IRB Leaders/Managers.

On June 27, 2013, Dr. Harold Perl organized and chaired a Roundtable session titled, "Planning the Way Forward for NIDA Prevention Science: Let's Ask the Most Important Research Questions So We Get the Most Useful Answers" at the 21st Annual Conference of the Society for Prevention Research in San Francisco, CA.

On June 27-28, 2013, Dr. Harold Perl served on the faculty for the 2013 NIH Regional Seminar on Program Funding and Grants Administration, in Baltimore, MD. He taught two workshops titled, "Primetime with Program, Understanding RPGs," and "Working with NIH Program Official Pre and Post Award". He also hosted a discussion on "Behavioral and Social Science Research at NIH" and provided 1:1 technical assistance for prospective NIH applicants.

On April 25-26, 2013, Dr. Dionne Jones, DESPR, Services Research Branch, participated in the NIDA Special Populations Research Development Seminar Series Workshop with Mock Review (Part 2), serving as a mentor to several junior investigators and providing guidance on their draft applications.

On May 28-31, 2013, Drs. Jacqueline Lloyd and Belinda Sims, DESPR, Prevention Research Branch, organized a roundtable titled "The Role of Cultural Adaptation in Dissemination and Implementation Research " at the 2013 21st Annual Society for Prevention Research Meeting held in San Francisco, CA. The panelists included: Dr. Jacqueline Lloyd, Chair; discussants Dr. Belinda Sims; Dr. Felipe Gonzalez Castro, University of Texas at El Paso; Moushumi Beltangady, Administration for Children and Families; Dr. Nancy A. Gonzales, Arizona State University; and, Dr. Nancy Whitesell, University of Colorado Denver.

On May 28-31, 2013, Drs. Jacqueline Lloyd and Brenda Miller, Pacific Institute for Research and Evaluation (PIRE) organized a roundtable titled "Domestic and International Strategies for Prevention Research On Young Adult High Risk Behaviors in Drinking Establishments" at the 2013 21st Annual Society for Prevention Research Meeting held in San Francisco, CA. The panelists included: Dr. Jacqueline Lloyd, Chair; Dr. Marcia S. Scott, NIAAA, Discussant; Dr. Brenda A. Miller, PIRE; Dr. Ian W. Holloway, University of California, Los Angeles; Dr. Johanna Gripenberg, Karolinska Institutet (Stockholm, Sweden); and, Terrance Alan, California Music and Culture Association.

On May 28-31, 2013, Dr. Jacqueline Lloyd was discussant for a symposium titled "Young Adults in Transition: Connecting Basic Science and Application" at the 2013 21st Annual Society for Prevention Research Meeting held in San Francisco, CA. The Chair and organizer was Dr. Thomas Kelley, University of Kentucky. The presenters were Donald R. Lynam, Purdue University; Dr. Helene White, Rutgers University; and, Dr. Blair Beadnell, Prevention Research Institute and University of Washington.

On May 28-31, 2013, Dr. Belinda Sims participated in the Early Career Preventionist Network, Lunch-time presentation: Peaking behind the Doors of the NIH Grant Review Process 2.0, during the 21st Annual Meeting of the Society for Prevention Research, San Francisco, CA.

On May 28-31, 2013, Drs. Aria Crump and Belinda Sims, DESPR, Prevention Research Branch, NIDA, organized a session entitled Your Federal Grant Application—Practical Considerations for Lean Times, for the 21st Annual Meeting of the Society for Prevention Research, San Francisco, CA. Representatives from the following ICs and federal agencies participated: National Cancer Institute, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, National Institute of Mental Health, NIH/Office of Disease Prevention, Administration for Children and Families, Centers for Disease Control and Prevention

On May 28-31, 2013, Dr. Belinda Sims chaired a symposium entitled Implementation Issues: International Perspectives, during the 21st Annual Meeting of the Society for Prevention Research held in San Francisco, CA.

On May 28-31, 2013, Dr. Augusto Diana, DESPR, Prevention Research Branch, organized a session entitled, "Research in the Social and Environmental Determinant of Health: A Review and a Prevention Agenda," for the 21st Annual Meeting of the Society for Prevention Research, held in San Francisco, CA.

On May 28-31, 2013, Dr. Augusto Diana organized and moderated a session entitled, "Social Determinant of Health: Some History and Thoughts about the Future," for the 21st Annual Meeting of the Society for Prevention Research held in San Francisco, CA.

On May 28-31, 2013, Dr. Augusto Diana organized and moderated a session entitled, "Food and Beverage Marketing to Youth," for the 21st Annual Meeting of the Society for Prevention Research, held in San Francisco, CA.

In May 2013, Dr. Augusto Diana presented at a session entitled, "The Prevention of Prescription Drug Abuse," for SAMHSA's Partnerships for Success Grantees Workshop in Rockville, MD.

On May 30, 2013, Drs. Elizabeth Robertson, Belinda Sims, and Eve Reider, DESPR, Prevention Research Branch, organized and Dr. Robertson chaired a roundtable at the 21st Annual 2013 Society for Prevention Research Meeting that was held at the Hyatt Regency in San Francisco, CA. The roundtable was titled "Intervening in Early Childhood to Prevent Drug Abuse." The discussants were Drs. Karl G. Hill, University of Washington, David L. Olds, University of Colorado Denver, Nicholas S. Ialongo, Johns Hopkins University, Leslie Leve, Oregon Social Learning Center, and Naomi Stotland, University of California San Francisco.

On April 24, 2013, Dr. Eve Reider, DESPR, Prevention Research Branch, represents NIDA on a Federal Interagency Committee on Traumatic Brain Injury and attended by telephone in a meeting that was held at the National Opinion Research Center (NORC) in Bethesda, MD.

On May 28, 2013, Dr. Eve Reider was an organizer and theme reviewer for the 6th Annual NIDA International Poster Session, held at the 21st Annual Society for Prevention Research Annual Meeting held at the Hyatt Regency, in San Francisco, CA.

On May 28-31, 2013, Dr. Eve Reider was a member of the program planning committee for the 21st Annual Society for Prevention Research Annual Meeting that was held in San Francisco, CA. The theme for the meeting was "The Science of Prevention: Building a Comprehensive National Strategy for Well-Being."

On May 31, 2013, Dr. Eve Reider co-chaired with Drs. Leslie Leve, Ph.D., Oregon Social Learning Center, and George Howe, Ph.D., George Washington University, a plenary session and corresponding roundtable at the 21st Annual Society for Prevention Research Annual Meeting that was held May 31, 2013 at the Hyatt Regency in San Francisco, CA. The plenary session was titled "Common Pathways to and Impact on Disease Prevention and Health Promotion." Dr. Megan Gunnar, Regents Professor, Director, Institute of Child Development, and University of Minnesota, presented on "Early Life Stress: Basic Research on Common Pathways to Multiple Physical and Mental Health Outcomes." Dr. Irwin Sandler, PhD, Director, and Prevention Research Center, Arizona State University, presented on "Long-term Effects of Promoting Effective Parenting: Implications for Theory and Public Health." COL Carl Castro, Research Area Director, U.S. Army Medical Research and Materiel Command, presented on "Brief Mental Health Training to Enhance Psychological Health among Military Personnel: Implications for Policy."

Dr. Eve Reider was invited by Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) to serve as a subject matter expert for several of its In-Progress Reviews (IPR) of Defense Health Program funded research. The meetings included:

- The 4th Annual IPR on Resilience Prevention Research, August 27-28, 2013
- The 4th Annual IPR on Substance Abuse Research, September 24-25, 2013

- The 4th Annual IPR on Family Research, October 22-23, 2013.
- The 2nd annual IPR on PTSD Stigma/Barriers to Care and Accessing Solutions, September 11, 2013. Dr. Reider was invited to be a standing IPR committee panel member for this panel. .The meetings were scheduled to be held in Frederick, Maryland and conducted by Carl A. Castro, Ph.D., Colonel, U.S. Army, Director, and MOMRP.

On May 20, 2013, Dr. Peter Hartsock, DESPR, Epidemiology Research Branch, together with members of the Woodrow Wilson International Center for Peace's Center for Advanced Russian Studies, presented on the Russian health and demographic situation to the National Intelligence University, in Washington, D.C.

On May 28, 2013, Drs. Richard Jenkins and Eve Reider, DESPR, Prevention Research Branch, organized and presented at a full-day pre-conference workshop that was held at the 21st Annual 2013 Society for Prevention Research Meeting in San Francisco, CA. The workshop was titled "Synthesis across Multiple, Long-Term Outcomes of Prevention Interventions Delivered Early in Life among Lesbian, Gay, Bisexual and Transgendered Youth**."** The workshop was moderated by Drs. George Howe, George Washington University and Ron Stall, University of Pittsburgh. Presenters and discussants included: Judith B. Bradford, Ph.D., The Fenway Institute, Brian Mustanski, Ph.D., Northwestern University, Mark Hatzenbuehler, Columbia University, Elizabeth B. Robertson, Ph.D., National Institute on Drug Abuse, C. Hendricks Brown, Ph.D., University of Miami, Tatiana Perrino, Ph.D., University of Miami, George W. Howe, Ph.D., George Washington University, and David Mackinnon, PhD, Arizona State University.

On April 15, 2013, Dr. Peter Hartsock DESPR, Epidemilogy Research Branch, lectured at a global health and ethics class at Georgetown University. Topics included emerging disease threats, and navigating the NIH grant application held in Washington D.C.

Dr. Geetha Subramaniam, CCTN, spoke at a webinar targeting State Youth Treatment Coordinators, at the request of the National Association of State Alcohol and Drug Abuse Directors, Inc. (NASADAD), on April 17, 2013. Her talk was titled "Buprenorphine Treatment for Opioid Dependent Youth."

The 44th Annual Medical-Scientific Conference of the American Society of Addiction Medicine (ASAM) was held April 25-28, 2013 in Chicago, IL. Dr. Geetha Subramaniam and Dr. Jag Khalsa (NIDA) co-chaired an all-day symposium titled "Buprenorphine: New Formulations, Medication Combinations, Indications and Longitudinal Effects."

Dr. Geetha Subramaniam planned, chaired (and presented on behalf of one of the speakers) a symposium titled "Cannabis Use and Youth: Updates on Risk, Assessment and Treatment" at the Annual Meeting of the American Psychiatric Association (APA), held May 18-22, 2013 in San Francisco, CA.

The 34th Annual Meeting of the Society for Clinical Trials was held May 19-22, 2013 in Boston, Massachusetts. NIDA CCTN staff presented the following:

1) Dr. Paul Wakim and Michele Melia (Jaeb Center for Health Research) were co-instructors of a workshop on "Practical Statistical Reasoning in Clinical Trials for Non-Statisticians."
2) Dr. Paul Wakim and Dr. Paul Van Veldhuisen (EMMES) gave presentations in a panel titled "Public Use Datasets." They discussed the NIH requirements and the CTN Data Share as an example.
3) Carmen Rosa organized and presented a workshop titled "OMG, Facebook and Research can be BFFs, LOL! Using New Media Tools in the Design and Conduct of Clinical Trials." This workshop included presentations and demonstrations from Dr. Erin Winstanley (OV Node) and Dr. Gloria Miele (GNY Node) regarding using the internet and social media, as well as cell phones, for clinical trials recruitment, retention, data collection, dissemination and overall communications about trials. Lynn Simpson (Harvard CTSA) also gave a demonstration of an EDC currently designed to conduct secure data collection.
4) Carmen Rosa chaired and presented a session titled "Community Based Clinical Trials: Innovative Regulatory Procedures to Enhance Translation." The panel included Royce Sampson and Kimberly Pressley (SC Consortium Node), and they discussed issues and recommendations in conducting rigorous clinical trials in community settings, based on the CTN experience.

Dr. Geetha Subramaniam, at the request of June Sivilli, Office of Demand Reduction, ONDCP, gave a presentation to ONDCP staff on June 6, 2013, on "Opioid Treatment in Youth: An Update."

The 75th Annual Meeting of the College on Problems of Drug Dependence (CPDD) was held June 15-20, 2013 in San Diego, California. CTN international activities were discussed during the NIDA International Forum. NIDA CCTN staff presented the following:
1) Dr. Geetha Subramaniam gave a talk titled "Treatment Update: Youth with Opioid Use Disorder" at the SAMHSA-NIDA pre-conference session, titled "Medication Assisted Treatment for Substance Use Disorders: Research and Practice." Dr. Betty Tai, along with SAMHSA's Director Dr. H. Westley Clark, spoke at the Opening Plenary.
2) Dr. Geetha Subramanian chaired a workshop titled "What is SBIRT and Why?" In this session, presenters (Drs. Redonna Chandler, Geetha Subramanian, Gail D'Onofrio and Robert Ali) reviewed recent evidence, highlighted the need for more empirical data, and described new health information technology tools for substance use screening. Dr. Betty Tai discussed the Role of Health Information Technology in SBIRT.
3) Carmen Rosa and Dr. Petra Jacobs chaired a session titled "Using the Clinical Trials Network (CTN) Model to Improve Treatment." This session included presenters from Ukraine (CTN INVEST Fellow Dr. Sergey Dvoriak), Mexico (Dr. Rodrigo Marin, NIP) and Canada (Dr. Evan Wood, UBC & Dr. Nathalie Gendron, CIHR). They discussed the approaches and advances made towards establishing evidence-based treatments in drug abuse treatment centers in their countries. Drs. George Woody, Walter Ling and Betty Tai were the discussants.

Dr. Scott Chen, OEA co-organized and co-chaired the Scientific Program and Review Interest Group (SPRIG) Meeting -"Health Scientist Administrators' Career Development: Needs, Challenges, and Opportunities?" held at Rockledge II, Bethesda, MD. Panel members were John J. McGowan (NIAID), Richard Conroy (NIBIB), and Kristen Dunn-Thomason (NIH Training Center).

Dr. Antonello Bonci, Director, IRP, was speaker at the Swartz Symposium on Reinforcement Learning at Yale University in April, 2013.

Dr. Antonello Bonci spoke in May 2013 at the Therapeutics Discovery Symposia on Optogenetics 2013 meeting in Boston, where he received the award for the topic of "Optogenetics approaches to synaptic plasticity and substance abuse"

Dr. Bruce Hope, IRP, gave an invited lecture at McLean Hospital in Belmont, MA.

Dr. Bruce Hope was one of the main speakers at a NIAAA workshop to discuss cutting edge technologies for studying specific cell types in behavior, with particular emphasis on the his work assessing activated Fos-expressing neuronal ensembles in behavior.

Dr. Amy Newman, IRP, gave invited lectures at University of North Dakota School of Medicine and Health Sciences, Department of Biochemistry and Molecular Biology, Grand Forks, ND and Johns Hopkins University, Department of Chemistry, Baltimore, MD.

Dr. Michael Baumann, IRP, co-chaired the opening session, and give a presentation, at the NIDA-sponsored workshop entitled, "Emerging Trends in the Abuse of Designer Drugs and Their Catastrophic Health Effects", held at NIDA Headquarters in Rockville MD, on July 26, 2013. His talk, "SAR of newly-emerging cathinone analogs at monoamine transporters", was part of a session devoted to the latest research on synthetic stimulant drugs.

Dr. Gianluigi Tanda, IRP, presented a talk entitled 'How does reinforcement work in the brain?' as part of the NIDA IRP Science for Nonscientists Seminar Series that is videocast to NIDA HQ.

Dr. Amina Woods, IRP, chaired the session on "Therapeutic Aspects of Molecular and Cellular Neuroscience" at the 2nd International Conference on Neurology and Therapeutics in Chicago and gave a lecture on "Phosphorylation Control of GPCR Heteromerization through Adenylate Cyclase" at the same conference.

Dr. David Gorelick gave an invited lecture on "Medications to treat cannabis use disorders" at the American Psychiatric Association 166th annual meeting, San Francisco, CA, in May 2013.

Dr. Marilyn Huestis, IRP, was an invited speaker at the Emerging Trends in Synthetic Drugs Workshop hosted by the National Institute of Standards and Technology on April 30, 2013. The title of her lecture was "Pharmacology of Synthetic Drugs." Dr. Huestis is an integral part of the NIDA-IRP's Designer Drug Initiative, a major component of her current research, addressing this important public health and safety problem.

Dr. Elliot Stein, IRP, was an invited speaker at the NIH Clinical Center where he gave Grand Rounds in June 2013 on "Genetic Neuroimaging Biomarkers of Nicotine Addiction."

Dr. Elliot Stein spoke at the University of Vermont, Grand Rounds, Department of Psychiatry in April 2013 on "Can resting state functional connectivity serve as a biomarker of drug addiction?"

Dr. Jean Lud Cadet, IRP, attended the Biological Psychiatry Meeting held in San Diego, California where he presented "Chronic, but Not Acute, Methamphetamine Exposure Decreases the Expression of Glutamate AMPA Receptors by Causing Hypoacetylation of Histone H4 in the Dorsal Striatum" on May 18, 2013.

Dr. Jean Lud Cadet presented "Epigenetic Basis of Methamphetamine-Induced Changes in Glutamate Function" at the National Institute on Environmental Health Sciences on June 7, 2013 at the Research Triangle Park.

Dr. Yavin Shaham, IRP, gave an invited lecture at Virginia Commonwealth Universityin Richmond, VA.

Dr Geoffrey Schoenbaum, IRP, spoke to students and faculty of the UNC MD/PhD program.

PLANNED MEETINGS

American Academy of Child and Adolescent Psychiatry (AACAP) Annual Meeting - Orlando, Florida - October 22-27, 2013. NIDA involvement at AACAP provides staff the opportunity to share and discuss cutting-edge addiction science information with child and adolescent psychiatrists, medical students and residents from around the country and across disciplines. These collaborations further our public health goals of broadly disseminating research results to improve substance use prevention and treatment in adolescents. NIDA is participating in several sessions at this year's meeting, including topics on understanding ADHD and smoking; medication therapies for youth with alcohol and other substance use disorders as well as a grant writing workshop.

Society for Neuroscience (SfN) Annual Meeting – San Diego, CA - November 9-13, 2013.

- November 8, 2013 - NIDA is planning to hold **Frontiers in Addiction Research Mini-convention** at the Westin Hotel in the Gas Lamp Quarter in San Diego (pending official approvals) as a Satellite Session of the SfN. The proposed sessions include: Emerging and Novel Aspects of Neuronal Transmission; the Jacob P. Waletzky Memorial Lecture; Extracellular RNAs in Neuroscience: Biology, Biomarkers, and Therapeutics; Advances in High Resolution and Large Scale Imaging of Brain Networks and Circuits; and the Role of the Basal Ganglia in Addiction.

- November 9-13, 2013 - NIDA will be participating in the **NIH Neuroscience exhibit booth.**

- November 11, 2013 - NIDA will be holding the workshop **Transitioning Beyond the Postdoc: Workshop for Early Career Investigators**

- November 12, 2013 – NIDA will be hosting the mini-symposium **New Insights into the Specificity and Plasticity of Reward and Aversion Encoding in the Mesolimbic System**.

Drs. James Bjork and Steven Grant of DCNBR organized and will co-chair a panel entitled "Legal Damages: New Insights into Chronic Marijuana Effects on Human Brain Structure and Function" at the **American College of Neurosychopharmacology Annual Meeting** to be held (pending official approval) December 7-12, 2013 in Hollywood, Florida.

STAFF HIGHLIGHTS

Staff Honors and Awards

2013 NIDA Director's Innovator Award (OD)
Massoud Vahbzadeh, PhD, IRP

2013 NIDA Director's Award of Merit
Individual Awards
Mary Ellen Michel, PhD, CCTN
Albert Avila, PhD, DBNBR
Samia Noursi, PhD, DBNBR
Lori Ducharme, PhD, DESPR
Bethany Deeds, PhD, DESPR
Sara Duffy, PhD, DESPR
Hirsch Davis, MA, DPMCDA
Lyle Furr, OEA
John Hamill, OM
Kenneth Goodling, OM
Said Kourrich, PhD, IRP
Marilyn Heustis, PhD, IRP

Group Awards
CCTN Budget Team
Carol Cushing, RN, CCTN
Ronald Dobbins, MBA, CCTN

Nicotine Research Cigarette Team for the NIDA Drug Supply Program (DBNBR)
Kevin Gormley, DBNBR
Brian O'Laughlin, OM
Rao Rapaka, PhD, DBNBR
Hari Singh, PhD, DBNBR

MTA Federal Leadership Team (DCNBR)
Cheryl Boyce, PhD, DCNBR
Barbara Usher, PhD, DCNBR
Joseph Frascella, PhD, DCNBR
James Bjork, PhD, DCNBR
Jurij Mojsiak, PhD, DPMCDA
Wilson Compton, MD, DESPR
Kevin Conway, PhD, DESPR
Redonna Chandler, PhD, DESPR
Kenneth Goodling, OM
Naimah Weinberg, MD, DESPR

Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) Research Team (DESPR)
Redonna Chandler, PhD, DESPR
Lori Ducharme, PhD, DESPR
Tisha Wiley, PhD, DESPR
Sara Duffy, PhD, DESPR
Dionne Jones, PhD, DESPR

STTR Data Harmonization Team (DESPR)
Redonna Chandler, PhD, DESPR
Will Aklin, PhD, DCNBR
Richard Jenkins, PhD, DCNBR
Dionne Jones, PhD, DESPR
Shoshana Kahana, PhD, DESPR
Jacqueline Lloyd, PhD, DESPR

The TRIAD Team (OD)
Carol Alderson, OM
Pamela Fleming, OM
Denise Pintello, PhD, OD
David Shurleff, PhD, OD
Mark Swieter, PhD, OEA

The NIDA Small Business Innovative Research (SBIR) Coordinating Committee (OD)
Will Aklin, PhD, DCNBR
Kristopher Bough, PhD, DPMCDA
Scott Chen, PhD, OEA
Augusto Diana, PhD, DESPR
Elena Koustova, PhD, OD
Brian O'Laughlin, OM
Quandra Scudder, CCTN
Dale Weiss, OD

All OEA Staff (OEA)
Kate Bent, PhD, OEA
Tonya Barnett, OEA
Loretta Beuchett, OEA
Scott Chen, PhD, OEA
Julius Diggs, OEA
Sonya Freeman, OEA
Lyler Furr, OEA
Jason Hill, OEA
Camilla Holland, OEA
Angelina Jordan, OEA
Eliane Lazar-Wesley, PhD, OEA
Minna Liang, PhD, OEA
Gerald McLaughlin, PhD, OEA

Cikena Reid, OEA
Nadine Rogers, PhD, OEA
Natisha Rowe, OEA
Jose Ruiz, PhD, OEA

The NIDAMED Clinician Education Team (OSPC)
Elisabeth Davis, MPH, OSCP
Carol Krause, MA, OSPC
Gaya Dowling, PhD, OSPC
Richard Denisco, MD, DESPR
Ericka Boone, PhD, OSPC
Robert Carroll, OSPC
Denise Crute, OSPC
Jane Lowers, OSPC
Vera Nordalm, OSPC

NIDA Chat Day Team (OSPC)
Carol Krause, MA, OSPC
Will Aklin, PhD, DCNBR
David Anderson, OSPC
Josie Anderson, OSPC
Ruben Baler, PhD, OSPC
Chanel Barnhill, OM
James Bjork, PhD, DCNBR
Antonello Bonci, MD, IRP
Ericka Boone, PhD, OSPC
Krisopher Bough, PhD, DPMCDA
Redonna Chandler, PhD, DESPR
Christina Cord, OM
Jessica Cotto, OSPC
Aria Crump, PhD, DESPR
Elisabeth Davis, MPH, OSPC
Bethany Deeds, PhD, DESPR
Richard Denisco, MD, DESPR
Gayathri Dowling, PhD, OSPC
Lori Ducharme, PhD, DESPR
Jennifer Elcano, OSPC
Mark Fleming, OSPC
Jeseph Frascella, PhD, DCNBR
Sheri Grabus, OSPC
Steven Grant, PhD, DCNBR
Marilyn Huestis, PhD, IRP
Meena Karithanom, OSPC
Michelle Leff, MD, IRP
Marguerite Lewis, OM
Janet Linton, OSPC

Jan Lipkin, OSPC
Jacqueline Lloyd, PhD, DESPR
Anita LoMonico, OM
Marsha Lopez, PhD, DESPR
Brian Marquis, OSPC
Stephanie Older, OSPC
Lanette Palmquist, OSPC
Harold Perl, PhD, CCTN
Nancy Pilotte, PhD, DBNBR
Denise Pintello, PhD, OD
Michele Rankin, OSPC
Elizabeth Robertson, PhD, DESPR
Joni Rutter, PhD, DBNBR
Cathrine Sasek, PhD, OSPC
David Shurtleff, PhD, OD
Jane Smither, OSPC
Anthony Strader, OM
Isbelle Thibau, OSPC
David Thomas, PhD, DBNBR
Eric Wargo, PhD, OSPC
Susan Weiss, PhD, OD
Cora Lee Wetherington, PhD, DCNBR
Brandon White, OM
David White, PhD, DPMCDA
Berhane Yitbarek, OM

NIDA Administrative Management Team (IRP)
Thomas Haines, IRP
Susan Harrelson, MA, IRP
Debra Haynes, IRP
Timothy Kirkendall, IRP
John Kunzelman, IRP
Cassandra Matthews, IRP
Katrina Maynard, IRP
Karla McCullum, IRP
Ward Pettis, IRP
Mary Jane Robinson, IRP
Massound Vahabzadeh, PhD, IRP

2013 NIDA Director's Award for Plain Lanaguage Writing (OD)
The Family Checkup Team
Gayathri Dowling, PhD, OSPC
Jessica Cotto, MA, OSPC
Eric Wargo, PhD, OSPC
Beinda Sims, PhD, DESPR
Eve Reider, PhD, DESPR

Elizabeth Robertson, PhD, DESPR
Carol Krause, MA, OSPC
Jan Lipkin, OSPC
Joan Nolan, OSPC
Mark Fleming, MA, OSPC
Janet Linton, OSPC

2013 NIDA Director's Award for EEO, Diversity and Quality of Worklife (OD)
Katrina Maynard, IRP

Length of Service Awards -- 30 Years
David Daubert, OM
Anita LoMonico, OM
Cindy Ambriz, IRP
Ora Dillon Carter, IRP
Mary Pfeiffer, PhD, IRP
Jonathan Katz, PhD, IRP
Thomas Aigner, PhD, DBNBR
Betty Tai, PhD, CCTN

Length of Service Awards -- 40 Years
Deborah Wertz, OM
John Hamill, OM
Paul Hillery, PhD, DBNBR
Shiela Zichos, IRP

Other NIDA Staff Awards

Dr. Jennifer Bossert, IRP, received the NIDA-IRP mentor award.

Dr. Comfort Boateng, IRP, has received a travel award to attend the 2013 Gordon Research Conference on Catecholamines, in August 2013.

Dr. Jean Lud Cadet, IRP, received the 2013 Harvey J. Bullock, Jr. EEO Award on June 12, 2013 at the NIH Director's Awards Ceremony. This event honors NIH employees for the outstanding way that they support the mission of the NIH.

MAJ Marisol Castaneto, a doctoral student at CDM, is the winner of the Society of American Federal Medical Laboratory Scientists (SAFMLS) Officer Writer's award for her article "Bath Salts" and Beyond: A Mini-Review of the Next Breed of Designer Drugs." MAJ Castaneto was selected for the prestigious US Army fully sponsored doctoral program and she selected the University of Maryland Baltimore School of Medicine and is pursuing her research in CDM on the new designer drugs.

Dr. Redonna K. Chandler, DESPR, Services Research Branch, received a 2013 NIH Director's Award as a member of the NIH Pain Consortium's Centers of Excellence in Pain Education Team.

Dr. Redonna K. Chandler received the 2013 CPDD J. Michael Morrison Award in recognition of her outstanding contributions in the area of scientific administration related to drug abuse research.

Dr. Richard A. Denisco, MD, MPH, DESPR, Services Research Branch, received a 2013 NIH Director's Award as a member of the NIH Pain Consortium's Centers of Excellence in Pain Education Team.

Dr. Richard A. Denisco received a 2013 NIH Director's Award as a member of the NIDA CME – Medscape project for safe prescribing of opioids.

Ms. Rebecca Hartman, IRP, and **Dr. Marilyn Huestis**, IRP, were featured in a Clinical Chemistry podcast released this spring highlighting their recent publication entitled "Cannabis Effects on Driving Skills" in June 2013.

Dr. Thomas Keck, IRP, received the 2013 NIDA-IRP Postdoctoral Mentoring Award, a travel award to attend the 2013 International Neurochemistry meeting in Cancun, Mexico in April, and a 2014 NIH FARE Award.

Dr. Jag Khalsa, DPMCDA, has been invited to represent NIDA on the DHHS Viral Hepatitis Implementation Group (VHIG).

Dr. Vivek Kumar, IRP, received a 2014 NIH FARE Award.

Dr. Ivan Montoya, DPMCDA, received the 2013 NIH Director's Award in recognition of his exceptional contributions to the mission of the joint NIDA-NIAAA Clinical Research Program.

Dr. Amy Newman, IRP, received the 2013 NIDA-IRP Diversity Mentoring Award for Faculty.

Dr. Oluyomi Okunola-Bakare, IRP, was a 2014 NIH FARE Award recipient.

The Department of Health and Human Services created an Interagency Pain Research Coordinating Committee (IPRCC), under the Patient Protection and Affordable Care Act. The Office of the Assistant Secretary for Health, DHHS, charged the IPRCC, in cooperation with NIH, to create a comprehensive, population health level strategy for pain prevention, treatment, management, education, and research, as recommended in the IOM Report: Relieving Pain in America. **David A. Thomas, Ph.D.**, DBNBR, has been invited to serve on the Professional Education and Training sub-committee working on a portion of this effort.

Wilson Compton, Kevin Conway, Elizabeth Lambert, Kay Wanke, Genna Vullo, and Nahla Hilmi received the "Leveraging Collaboration Award" from the Commissioner of the Food and Drug Adminstration for Successfully Implementing the Field Test of the Joint NIDA/FDA PATH Study, June 2013

Staff Changes

New Employees

Lisa Coleman joins the NIDA COAC as the Deputy Director, OA, NIDA from NCI. Ms. Coleman has been a highly regarded Contracting Officer at NIAID, NICHD, and NCI. Ms. Coleman will assist the Director, OA, NIDA in overseeing COAC Acquisition Policy, Operations & Oversight.

Sean Dalenberg joined NIDA's Office of Acquisitions (OA) as a contract specialist in the NCATS Section of OA in July 2013. Sean comes to us from the DHHS Program Services Center (PSC) with several years of contracting experience as both a Contracting Officer and a Contracting Officer's Representative (COR).

Paula Peltier joined the Administrative Management Branch (AMB) in July 2013 as an Administrative Specialist. Paula is the new NIDA HQ point of contact for purchasing, payments, and policy guidance. She comes to us with over 20 years of experience in the administrative/procurement field, most recently with the NCI OD.

New Appointments/Transfers

Dr. Dave Thomas of the Division of Basic Neuroscience and Behavioral Research (DBNBR) is joining the Division of Clinical Neuroscience and Behavioral Research (DCNBR) as the Deputy Director. Dr. Thomas began his career at the National Institutes of Health (NIH) in 1984, working in the intramural pain research program at the then National Institute on Dental Research (now NIDCR) where he studied opioids, pain and analgesia in monkeys and rats, using behavioral, pharmacological and electrophysiological approaches. In 1995, Dr. Thomas joined the National Institute on Drug Abuse where he worked in the DBNBR. His program areas included pain and analgesia, opioids technologies and the abuse liability of analgesics. He is co-chair of NIDA Prescription Opioids and Pain workgroup, which fosters pain and opioid research and education. He is also an original and current member of the NIH Pain Consortium, which promotes pain research across the NIH, and he leads the NIH Pain Consortium's Centers of Excellence in Pain Education program, which promotes pain education in medical, nursing, pharmacy and dental schools. He will bring these many skills with him to DCNBR and will work to enhance interactions with the other Divisions and to promote the mission of NIDA.

Dr. Albert Avila is serving as Acting Director, Special Populations Office.

Dr. Minna Liang, OEA, was promoted to NIDA Referral Officer in July 2013.

Departures

Afomeya Agonafer, OD, left NIDA on July 27, 2013 to become a Secretary for the Deputy Director of NCCAM in the Office of the Director. Afomeya began her career at NIDA in 2002 in the Office of the Director/Executive Secretariat and in 2011, her exceptional administrative management skills were recognized by senior staff, which led to her serving as Secretary in the OD to the NIDA Deputy Director from 2011-2013. Afomeya is known for her superb organizational skills, poise and professionalism.

Tanya Barnett joined NIDA OEA as an extramural support assistant (ESA) in 2006 and progressed to Task Leader within DEAS and to Lead ESA position in 2012. She left NIDA for the Office of Disease Prevention (NIH OD) as Program Specialist in June 2013. Tanya served as ESA for NIDA Centers reviews and for many other complex NIDA reviews. Her professionalism, general good nature, writing, editing and database skills will be missed.

Dr. Kate Bent joined NIDA in late February 2013 as Deputy Director of NIDA OEA. She came to NIDA from CSR, where she had served as Chief of the Health Care Delivery and Methodologies IRG and more recently as Senior Advisor to the CSR Director. At NIDA OEA, Kate served as Acting Referral Officer, Privacy Act Coordinator, and clinicaltrials.com representative. Kate joined the FDA in July 2013 as an Assistant Commissioner for Policy.

Sonya Freeman who joined NIDA OEA as an ESA in 2006, was ESA for NIDA's training committee, aided many other NIDA reviews and also served as the office Purchasing and Travel specialist. In June 2013, she joined NHLBI's Office of Committee Management. Sonya was especially known for her work ethic, notable attention to details, organizational skills and persistence, as well as her marvelous laugh.

Khaled Gohar joined NIDA's Office of Acquisitions (OA) in February 2013 and transferred to SAMHSA in September 2013. During his tenure, Khaled worked for the NIMH Section of OA as a Contract Specialist.

Dr. Takato Hiranita, of the Molecular Targets & Medications Discovery Branch, of NIDA's Intramural Research Program (IRP), has accepted the position of Pharmacologist at the Food and Drug Administration, National Center for Toxicological Research, Jefferson, Arkansas

Dr. Diane Lawrence, former Associate Director of NIDA's AIDS Research Program, joined the National Institute of Allergy and Infectious Diseases' Pathogenesis and Basic Research Branch in June 2013. At NIAID she is managing grants and contracts that support basic and applied preclinical research.

Dr. Michael McDannald, of the Cellular Neurobiology Research Branch of NIDA's IRP, a recent K99 recipient, has received a tenure-track offer from MCG.

Bridget McDonald, an Administrative Services Agent in the Office of Management/Administrative Management Branch resigned on August 1, 2013.

Dr. Mary Ellen Michel, former Deputy Director of the CCTN, joined the National Center for Medical Rehabilitation Research (NCMRR) program at the National Institute of Child Health and Human Development (NICHD) in June 2013. At NICHD, she is managing clinical programs on head injury, stroke and rehabilitation. Dr. Petra Jacobs is serving as Acting Deputy Director, CCTN.

Fabienne Saint-Preux, IRP, has left the Molecular Neuropsychiatry Section as a Post-baccalaureate IRTA to attend medical school at Saint Louis University. Fabienne participated in NIDA IRP's Scientific Director's Fellowship for Diversity in Research (SDFDR). She started at NIDA-IRP in August 2011 and published a first author paper in April 2013.

Dr. Mariela Shirley, NIAAA, has served for over one year on a part time detail to facilitate collaborative initiatives on child and adolescent research and comorbidity with DCNBR and NIDA's Child and Adolescent Workgroup. She has recently taken a new position with NIH's Office of Women's Health as the Associate Director of Special Projects and Centers.

Dr. David Shurtleff, Acting Deputy Director, left NIDA on June 1, 2013 to become the Deputy Director of NCCAM. In his new position, he will play an important role in directing NCCAM's scientific, programmatic, and administrative initiatives. David's 18-year career at the NIH began at NIDA as a health scientist administrator in the Behavioral Sciences Research Branch. Within DBNBR, he served in various leadership roles: Acting Deputy Director of NIDA's Division of Neuroscience and Behavioral Research; the Division's Deputy Director; and from 2001 to 2011, he served as the Director of NIDA's Division of Basic Neuroscience and Behavioral Research. In January 2011, David assumed the position of Acting Deputy Director of NIDA and during his tenure, played an important role in the development, implementation, and management of the Institute's broad grant portfolio covering basic cellular, molecular, and systems neurobiology as well as behavior, treatment, medication development, clinical neuroscience, clinical trials, prevention, and health services research.

Dr. Jonathan Slezak, of the Molecular Targets & Medications Discovery Branch, IRP, has accepted the position of Assistant Professor at the Department of Psychology in the School of Natural Science and Mathematics at Mount St. Mary's University, Emmitsburg, Maryland.

Ingrid Tulloch, IRP, has left the Molecular Neuropsychiatry Section as a Postdoctoral Fellow to teach as a full-time Assistant Professor at Stevenson University in the Psychology Department.

Dr. Louise Wideroff of the Division of Basic Neuroscience and Behavioral Research has accepted a position for a promotion at the National Eye Institute where she will oversee programs in epidemiology. While at DBNBR, Dr. Wideroff handled a portion of the statistical genetics portfolio, coordinated the DBNBR SBIR program, and was the NIDA representative to the H3Africa program.

Retirements

Dr. Tom Aigner of the Division of Basic Neuroscience and Behavioral Research has retired after 31 years of federal government service. Dr. Aigner earned his B.S. degree in psychology/statistics and his M.S. in pharmacology at the University of Houston. He earned his Ph.D. in Pharmacology at the Medical College of Virginia. He was a postdoctoral fellow and research associate at the University of Chicago where he worked in the Department of Psychiatry under Charles Schuster and Chris Ellyn Johanson and then as a research associate in the Department of Surgery under Chris Zarins, M.D. Tom joined NIH in 1982 as an intramural staff scientist in Mortimer Mishkin's NIMH Laboratory of Neuropsychology. In 1995, Tom moved to his present position as a Health Scientist Administrator at NIDA, where he administers a portfolio of grants in neuroimaging in animals and nanotechnology. Dr. Aigner has published widely in the area of drug abuse and addiction with significant contributions in studies of the neuropsychopharmacology of memory and visual recognition in rats and non-human primates. Along with Weiss, S.R.B., and Post, R.M., Dr. Aigner holds Patent No. 4,942,182, (Treatment for cocaine addiction). Tom has represented NIDA on many NIH committees and work groups, has contributed a great deal to DBNBR and has been a creative presence in the division.

Garveyette Brown retired after a Federal career spanning thirty-nine years. Since 1965 she has held a wide variety of positions including Clerk-Typist at the U.S. Civil Service Commission, secretary at the U.S. House of Representatives and the U.S. Senate, Communications Industry Analyst at the Federal Communications Commission (FCC), and teacher of second and third grade students in the District of Columbia. Following all these positions, Garveyette joined the Federal Government, accepting a position as Program Assistant with NIDA/OSPC/PILB and NIDA/DESPR/OD where she has served until her retirement on August 31, 2013.

Dr. Teresa Levitin joined NIDA in 1996 as Deputy Director of the Office of Extramural Program Review after positions with NIMH and CSR. She became Director of OEPR (which was later renamed OEA) in 1997 and retired from federal service in February 2013. Teri's many contributions to NIDA included her numerous activities within NIDA OEA, across NIDA, and across NIH. Among many and various responsibilities, she served as Executive Secretary for NIDA Council, NIDA Research Integrity Officer, NIDA's EPMC representative, and as advisor and friend to many in the NIDA and NIH community. Teri's positive outlook, ability to create a nurturing and supportive workplace, focus on the quality of the work product, and her remarkable verbal, writing and editing skills, were gifts she willingly shared and will long be remembered for.

Donna Tolson, a Lead Administrative Officer in the Office of Management/Administrative Management Branch retired on May 31, 2013 after 36 years of service, the last 26 of which were with NIDA. During her tenure at NIDA, Donna made many significant administrative contributions, and received multiple awards and recognition for leading several IC initiatives and for her support of the NIDA Office of the Director.

GRANTEE HONORS

Dr. Karen Bierman, Professor, The Pennsylvania State University, received the 2013 Prevention Science Award from the Society for Prevention Research, in recognition of her work developing and testing prevention strategies.

Dr. Eric Brown, Research Assistant Professor, University of Washington, received the 2013 International Collaborative Prevention Research Award, for his contributions to the field of prevention science in the area of international collaboration.

Dr. Ben Cravatt was the recipient of the International Cannabinoid Research Society Mechoulam Award for 2012 and was presented with the honor at the 2013 Symposium as was not able to attend the meeting in 2012.

Dr. Antoine Douaihy of the CTN Appalachian Tri-State Node was chosen by the current students of the University of Pittsburgh School of Medicine to receive the Charles Watson Teaching Award. The Charles Watson Teaching Award recognizes a faculty clinician who best embodies the qualities of Dr. Charles Watson – a masterful clinician, academician, caretaker of his patients, educator, mentor, and contributor to the medical school community and community at large. This award was presented at the AOA Induction Banquet on April 23, 2013.

Dr. Mahmoud ElSohly received the Lifetime Achievement Award, 2013 from the International Cannabinoid Research Society.

Dr. Brian Flay, Professor, Oregon State University, received the 2013 Friend of ECPN (Early Career Preventionist Network) award from the Society for Prevention Research, in recognition of his support and encouragement of early career prevention scientists or issues.

Dr. Mark Greenberg, Professor, The Pennsylvania State University, received the 2013 Presidential Award of the Society for Prevention Research, in recognition of his lifetime contribution to prevention science research.

On June 6-8, 2-13, **Dr. Brian M. Hicks**, Research Assistant Professor of Psychiatry at the University of Michigan, was recognized with the Early Career Contributions Award at the 5th biennial meeting of the Society for the Scientific Study of Psychopathy that met in Washington, DC.

Researchers from the CTN Florida Node Alliance (FNA) led by Executive Director, **Dr. Viviana Horigian**, were recognized by the National Institute of Psychiatry in Mexico for successfully completing the first phase of a groundbreaking collaboration involving the transfer of technology for clinical trials implementation. Dr. María Elena Medina-Mora, General Director of the National Institute of Psychiatry "Ramón de la Fuente" presented the award during a ceremony celebrating the completion of the first randomized study conducted as part

of a nationwide clinical trials network of substance abuse and mental health researchers and community treatment providers.

Dr. Aron Lichtmann was the recipient of Mechuolam Award for the ICRS 2013.

Dr. Patricia Penn, a long-time member of the CTN Western States Node (and of the original California-Arizona Node) is the recipient of a Let's Get Better Together Lifetime Achievement Award from the LGBTQ Behavioral Health Coalition of Southern Arizona and the LGBTQ Consortium. The award is given to individuals who have demonstrated exceptional leadership and innovation in serving the behavioral health needs of LGBTQ individuals and families. Dr. Penn is the Site PI for La Frontera Center in Tucson, Arizona, an original CTN community treatment program, which has been a successful site for CTN clinical trials CTN 0014 (BSFT), CTN 0032 (HIV Rapid Testing), and CTN 0046 (Smoking Cessation). She is being honored for her work with LBGTQ populations over the years and received the award on April 5, 2013 at the 2013 Let's Get Better Together Conference.

Dr. Louise Rohrbach, Associate Professor, University of Southern California and **Dr. Richard Spoth**, Senior Prevention Scientist, Iowa State University, were named the 2013 co-recipients of the Service to SPR Award, in recognition of their outstanding service to the organization, which involved co-chairing the Mapping Advances in Prevention Science (MAPS) Type 2 Translational Research Task Force.

Dr. Helene White, Professor, Rutgers University, received the 2013 Translational Science Award from the Society for Prevention Research, in recognition of her contributions to the field of prevention science in the area of Type 1 or Type 2 translational research.

The entire inaugural cohort of **Fellows of the Society for Prevention Research** included current or past NIDA grantees. Fellows were accepted in recognition of their distinguished record of research reflecting a body of work that has had a broad and significant impact on prevention science. Nine Fellows were accepted into the 2013 inaugural cohort: **Dr. Gilbert Botvin**, Professor Emeritus, Weill Cornell Medical College; **Dr. Patricia Chamberlain**, Senior Research Scientist, Oregon Social Learning Center; **Dr. J. David Hawkins**, Professor, University of Washington; **Dr. Sheppard Kellam**, Professor Emeritus, Johns Hopkins University; **Dr. David MacKinnon**, Professor, Arizona State University; **Dr. David Olds**, Professor, University of Colorado, Denver; **Dr. Irwin Sandler**, Professor, Arizona State University; **Dr. Zili Sloboda**, Consultant, JBS International, Inc.; **Dr. Patrick Tolan**, Professor, University of Virginia.